ELECTROENCEPHALOGRAPHY
AND
CLINICAL NEUROPHYSIOLOGY

AN INTERNATIONAL JOURNAL

Vol. 11, Number 3 August 1959

HIPPOCAMPAL ELECTRICAL ACTIVITY DURING THE DEVELOPMENT OF CONDITIONED REFLEXES

E. GRASTYÁN, M.D., K. LISSÁK, M.D., I. MADARÁSZ M.D. and H. DONHOFFER, M.D.

Institute of Physiology, University Medical School Pécs, Hungary

(Received for publication: September 26, 1958)

In 1954 Green and Arduini made the important observation that an inverse relationship exists between the activity of the hippocampus and that of the neocortex i.e. a stimulus which causes arousal and desynchronization of the activity of the neocortex would elicit rhythmic slow waves from the hippocampus. As early as 1938 a similar observation was made by Jung and Kornmüller in the rabbit in connection with painful, and occasionally, auditory stimuli. Recently these findings have been confirmed by several authors (Liberson and Cadilhac 1954. Liberson and Akert 1955; Cadilhac 1955; MacLean *et al.* 1955; Rimbaud, Passouant and Cadilhac 1955). However, the significance of the inverse hippocampal response has not yet fully been elucidated. From the fact that in the majority of cases hippocampal slow potentials and neocortical desynchronization appear simultaneously, Green and Arduini (1954) inferred that the synchronized response was an indication of a peculiar form of hippocampal activation, the so-called arousal reaction. At the same time they pointed out that the simultaneous appearance of the two forms of activity, although frequent, was not invariable.

When studying the hippocampal electrical changes accompanying habituation we found that at the establishment of habituation, i.e. when the inhibitory process had been stabilized, it was the desynchronized pattern that became the regular response for a definite period of time. This observation seemed of importance for the interpretation of the slow response. In order to analyse behavioural processes more precisely and objectively we passed on to the study of conditioned reflexes.

The experiments to be described below have led to the conclusion that the rhythmic slow response of the hippocampus is an early sign of the appearance of a temporary connection and, therefore, cannot simply be regarded as a peculiar form of hippocampal activation or arousal.

METHODS

The observations were made on 15 adult cats. The electrical changes were analysed with chronically implanted electrodes during the elaboration of alimentary and defensive motor conditioned reflexes. Conditioning was only begun after implantation of the electrodes and complete recovery of the animals.

In 10 of the animals only the alimentary reflex was elaborated and in 5, in addition, also the defensive conditioned reflex. In 4 of the latter 5 animals the alimentary, and in one the defensive conditioned reflex was first established. The duration of an experiment generally varied from one to three months. Simultaneously with the EEG recording motion pictures were taken of the characteristic stages of the experiments. At the end of the experiments the sites of recording were checked also by stimulation at different phases of the conditioned reaction.

Elaboration of the conditioned reactions.

The alimentary conditioned reflex was elaborated in the apparatus shown in figure 1 A. As conditioned stimuli, sounds of different pitch produced by a generator were used. The experiments were preceded by a checking of the influence of the different stimuli on the electrical activity, after which the animals were taught how to get the food from the feeding device. Only then was the association of the sound stimulus and feeding commenced. The first traces of the conditioned reflex generally appeared after 5 to 20 associations, the necessary number of associations changing with the animals.

The defensive conditioned reflex was elaborated in another apparatus seen in figure 1 B, its development being essentially the same as that of the alimentary reflex. For a more detailed description of the elaboration of the conditioned reflexes the reader is referred to a previous communication (Grastyán, Lissák and Kékesi 1956).

Recording of the Electrical Activity. Recordings of the hippocampal activity were obtained by means of silver electrodes, using a bipolar technique. The electrodes were enamel-coated to about 0.5 mm. of their tips, which were spaced 1.5 mm. apart. When monopolar records were taken the indifferent electrode was placed in the midline of the occipital protuberance. The deep electrodes were implanted with the aid of a stereotaxic instrument and fixed to the skull with dental cement. Cortical activity was recorded with epidurally placed bipolar silver ball electrodes with the tips spaced 2-3 mm. apart. The terminals of the electrodes were soldered to the poles of a miniature socket which was fixed to the top of the skull with "Duracryl", insulating the poles from one another as well as from the surrounding tissues. The connection between the animal and the recording apparatus was secured by means of a light,

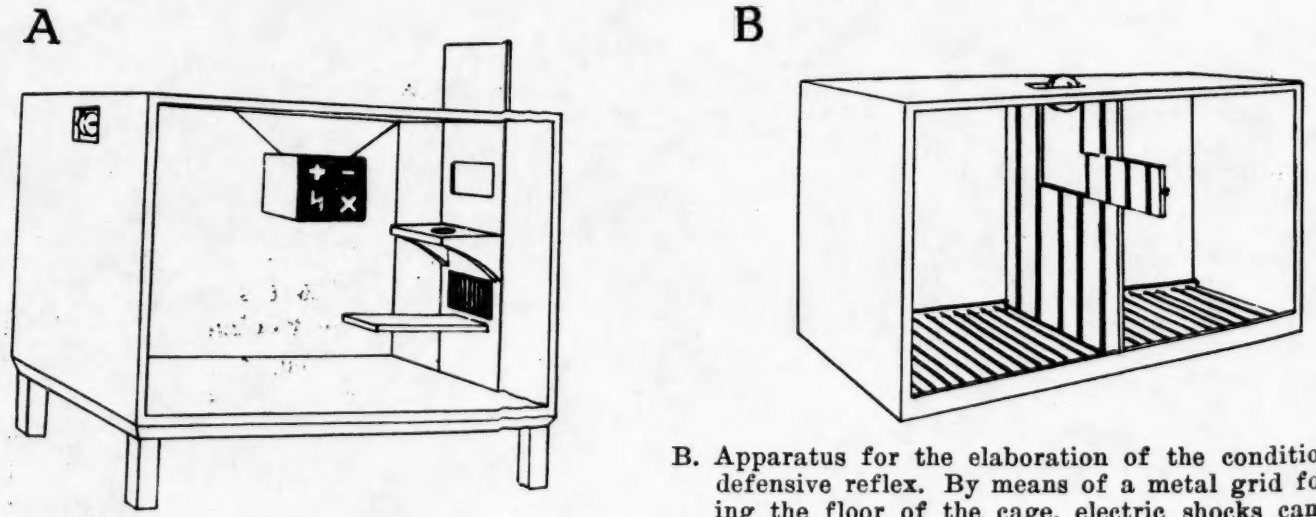


Fig. 1

A. Cage for the elaboration of the alimentary conditioned reflex. The feeding device is seen attached to the right wall of the cage; the signals flashed by the box suspended from the ceiling indicate on the motion pictures, the kind of stimulus being applied.

B. Apparatus for the elaboration of the conditioned defensive reflex. By means of a metal grid forming the floor of the cage, electric shocks can be applied to the animal's paws, upon which the animal will flee to the other identically built compartment.

flexible cable (the leading wires contained in a surgical thread). Slight tension in the cable suspended from a roll on the ceiling of the cage was maintained by a weight of a few grams attached to its distal end. This arrangement enabled the animals to move about freely.

Potentials were recorded by a 6-channel Kaiser, and a 4-channel Schwartzer apparatus. Four pairs of electrodes were implanted in each of the animals. In 10 animals 2 pairs of electrodes were placed in different regions of the hippocampus and in 4 animals, in addition to the hippocampus, also in the mesencephalic reticular formation. The cortical electrodes were located over the motor, the somatosensory and the auditory cortices and, in two cases, also over the occipital cortex. The sites of recording in the hippocampus and in the reticular formation were identified histologically at the end of the experiments (Nissl stained section).

RESULTS

Effects Observed at the First Application of Indifferent Stimuli. At the beginning of our experiments no special attention was paid to the responses to the first application of indifferent stimuli because it had been expected that the stimuli would produce the characteristic rhythmic slow waves described by Green and Arduini (1954). In the majority of cases the activity of the hippocampus was checked with familiar stimuli of an affective character, generally used with cats (''puss !'', ''shoo !''). These stimuli invariably elicited from the hippocampus the characteristic type of rhythmic slow waves (fig. 2 A). In some animals, however, we were surprised to find that under identical experimental conditions and with identical background activity, entirely unknown stimuli (e.g. clicks of different frequencies) did not evoke the typical slow response from the hippocampus but, just as in the case of the neocortex, desynchronization (fig. 2 C and 4 A). This desynchronization was chiefly characterized by the disappearance of the slow waves and by a decrease of the amplitude of the hippocampal activity; the increase in the number of discharges was, however, not so pronounced or in some cases difficult to observe. The background activity of the hippocampus is rather complex, fast (16-30 c/sec.) and slow (4-7 c/sec.) components varying at irregular intervals and many fast components with slow amplitude being superimposed on the high voltage slow waves. Occasionally the superimposed fast discharges made it difficult to define the exact frequency of the background activity. Even in the cases which were easy to analyse the increase in frequency proved to be relatively low, generally not exceeding 15-20 per cent. Later the electrical changes produced by the first application of various stimuli were examined systematically and it was found that presumably unknown or indifferent stimuli caused desynchronization in the great majority of the animals.

The electrical changes (desynchronization and slow waves) were also accompanied by characteristic somatic manifestations. If the stimulus (e.g. a familiar calling sound, ''puss'') elicited the special slow potentials, the animal reacted with tonic orientative (searching) movements. When the stimulus desynchronized the activity of the hippocampus the animal occasionally remained completely motionless and in other cases performed a short, phasic, orientative movement of the head towards the sound.

The early stage of development of the conditioned reflex. The electrical changes observed during the development of the alimentary conditioned reflex and during that of the defensive conditioned reflex, respectively, were essentially identical (except for a slight difference in time) and will, therefore, be discussed together.

In the course of the development of the conditioned reflex marked changes may be observed in the electrical activity of the hippocampus. During the associations of the conditioned and unconditioned stimuli the above mentioned initial desynchronization becomes more and more uncharacteristic. Under the influence of the conditioned signal slow waves make their appearance at the beginning less and later more and more definitely until, eventually, the characteristic slow activity (4-7 c/sec.) dominates the picture (fig. 3 A,

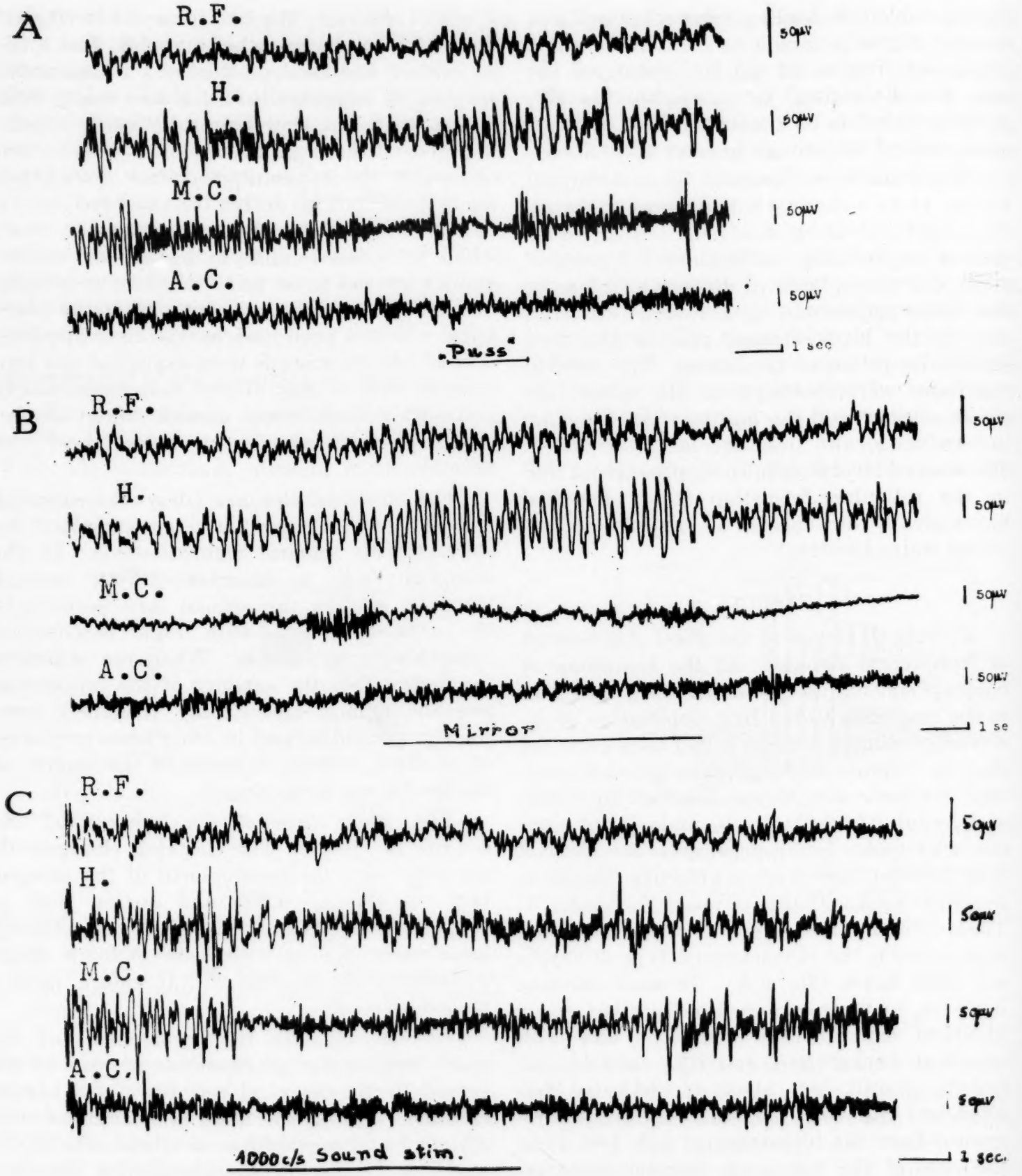


Fig. 2

Cat M.4. Changes accompanying the elaboration of the defensive conditioned reflex. Abbreviations: R.F.: Reticular formation. H.: Hippocampus. M.C.: Motor cortex. A.C.: Auditory cortex.

A. A familiar calling sound stimulus (''puss'') elicits the rhythmic slow (5 c/sec.) response.
B. A similar marked change is seen when the animal looks in a mirror.
C. At its first application the indifferent sound stimulus (1000 c/sec.) desynchronizes the activity of the hippocampus and that of the neocortex.

4 B, 4 C, and 6 A). At the same time neocortical activity continues to be desynchronized.

These electrical changes are also accompanied by characteristic somatic manifestations. While formerly the stimulus only elicited a single movement of the head or no response at all, it now evoked pronounced tonic orientative (searching movements. In some of the cases the movement was definitely directed towards the source of the conditioned stimulus (loud-speaker) as early as after the first associations, in other cases, however, it was quite inadequate or purposeless and had no connection with the conditioned reaction indicated by the stimulus (e.g. in the case of the alimentary conditioned reflex the conditioned stimulus caused the animal to run in a direction opposite to that of the feeding device). Later these purposeless, diffuse motor reactions decreased in number more and more and the movements, like special orientative movements, became more and more definitely directed towards the source of the conditioned stimulus.

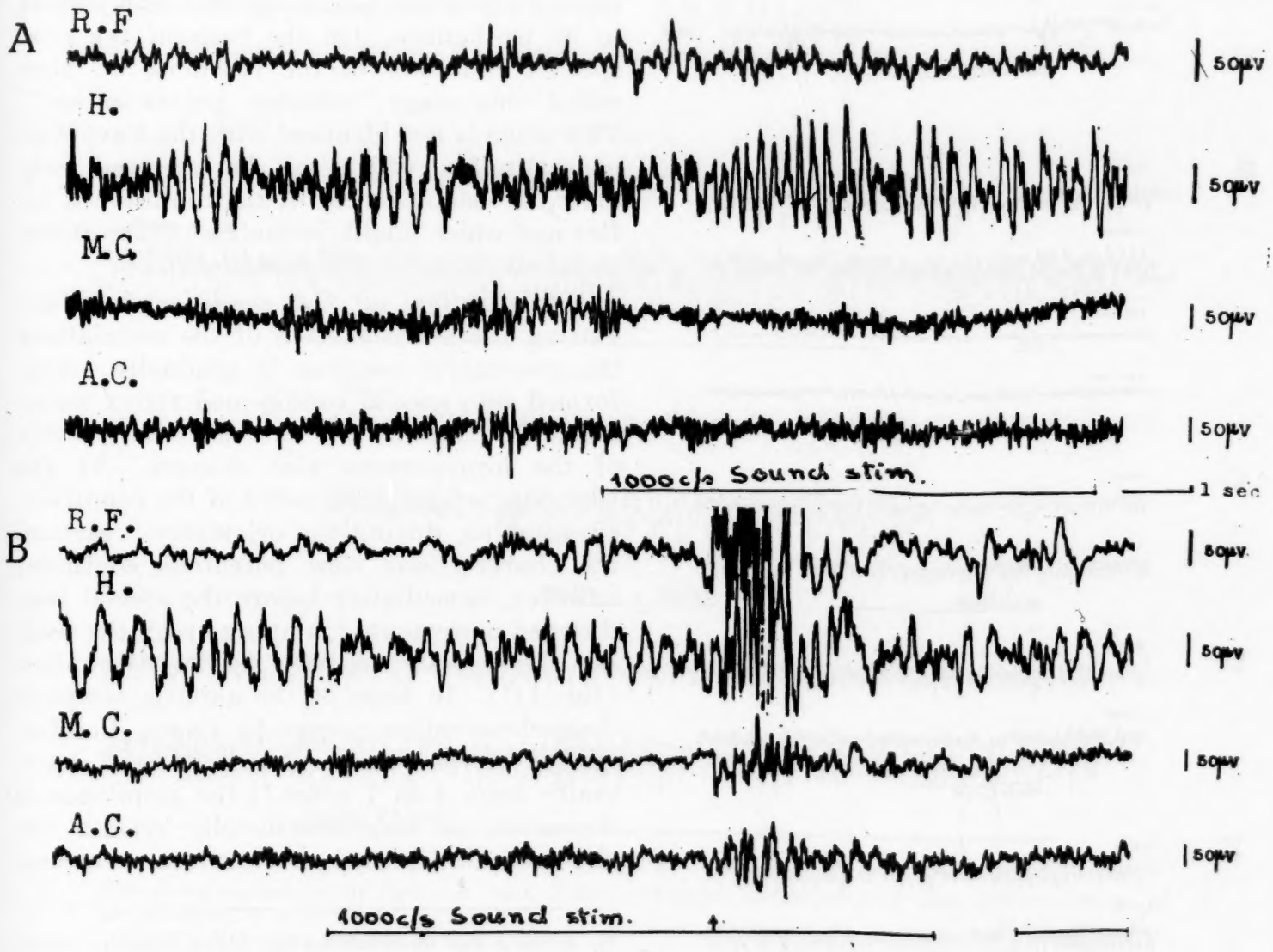


Fig. 3

A. A few associations of the formerly indifferent sound stimulus with an electric shock evokes a vigorous orientative reaction and slow potentials (5 c/sec.) in the hippocampus.
B. At the appearance of the conditioned defensive reflex the stimulus begins to desynchronize hippocampal activity again. Arrow: of the conditioned motor reaction.

The earliest stage in the development of the temporary connection is, therefore, characterized by nonspecific motor reactions. Before eliciting the specific conditioned reflex, the conditioned stimulus evokes, temporarily, purposeless, diffuse movements or orientative, searching movements. The duration of this

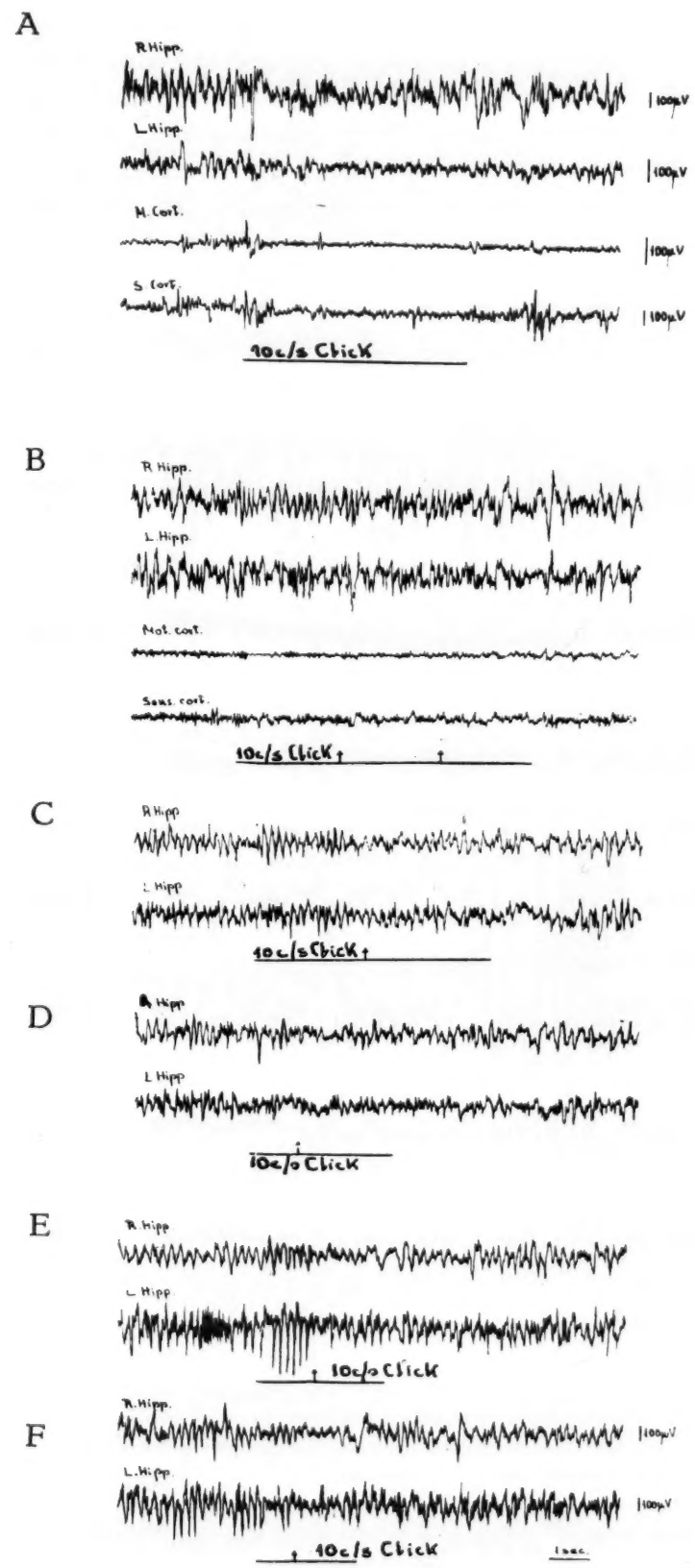


Fig. 4

Cat H.28. Changes of the electrical activity during the elaboration of the alimentary conditioned reflex. Abbreviations: R. Hipp.: Right hippocampus; L. Hipp.: Left hippocampus. M. Cort.: Motor cortex. S. Cort.: Somatosensory cortex.

A. At its first application an indifferent sound stimulus (10 c/sec. click) desynchronizes the activity of the hippocampus as well as that of the neocortex.

reaction is variable and may occasionally be short, however, it will invariably manifest itself before the appearance of the specific response. The simultaneous characteristic electrical changes of the hippocampus suggest, that these manifestations express a peculiar, early stage of development of the temporary connections which is also uniform with respect to its mechanism. On the basis of the non-specific character of the reactions we have called this stage "effector generalization". This stage is not identical with the Pavlovian generalization which can be observed only after the establishment of the conditioned reflex and which might, in contrast to the above, be called "sensory generalization".

Stabilization of the conditioned reflex. During further repetition of the associations the orientative reaction is gradually transformed into special conditioned reflex movements. Simultaneously the electrical activity of the hippocampus also changes. At the beginning of the application of the conditioned stimulus, during the orientative reaction, the characteristic slow potentials continue; however, immediately before the special conditioned movements (jumping up on the feeding device) the activity is desynchronized (fig. 4 C). In some of the animals complete desynchronization occurs in stages, the frequency of the slow waves is increased (generally from 4 to 7 c/sec.), the amplitude is decreased, or may occasionally remain unchanged, the individual slow waves become

B. After a few associations the above stimulus elicits rhythmic slow waves from the hippocampus but continues to desynchronize the neocortex. First arrow: food is shown to the animal. Second arrow: feeding.

C. First elicitation of the conditioned reflex by the 10 c/sec. click. Arrow: beginning of the motor reaction.

D. The conditioned reflex has been stabilized. Desynchronization is elicited at once, the orientative reflex has disappeared, latency of the reflex shortened.

E. If the stimulus finds the animal in an unusual position, the slow response (7 c/sec.) will reappear again. Note that the slow waves show a spike-like character.

F. The subsequent stimulus which finds the animal in its usual position causes desynchronization. The solid line at the bottom indicates the duration of the stimulus.

shorter in duration, i.e. the waves assume an almost spike-like character (fig. 4 E). The passing of the orientative reaction into a special conditioned reflex movement was in some cases very definite and easily distinguished by direct observation. However, in other animals it was so subtle and gradual that it could only be followed by an analysis of the motion pictures, in which it was found that the hippocampal slow potentials indicated the orientative reflex (searching movements) with perfect accuracy (fig. 8).

In the course of further associations the duration of the orientative movements and, at the same time, the latency of the conditioned reflex become shorter and shorter and the desynchronized period approaches the beginning of the stimulus more and more. Finally, in the majority of animals the orientative reflex disappears completely and the sound stimulus will readily elicit the special conditioned movements and simultaneous desynchronization from the hippocampus (fig. 6 B, 3 B, 4 D and F).

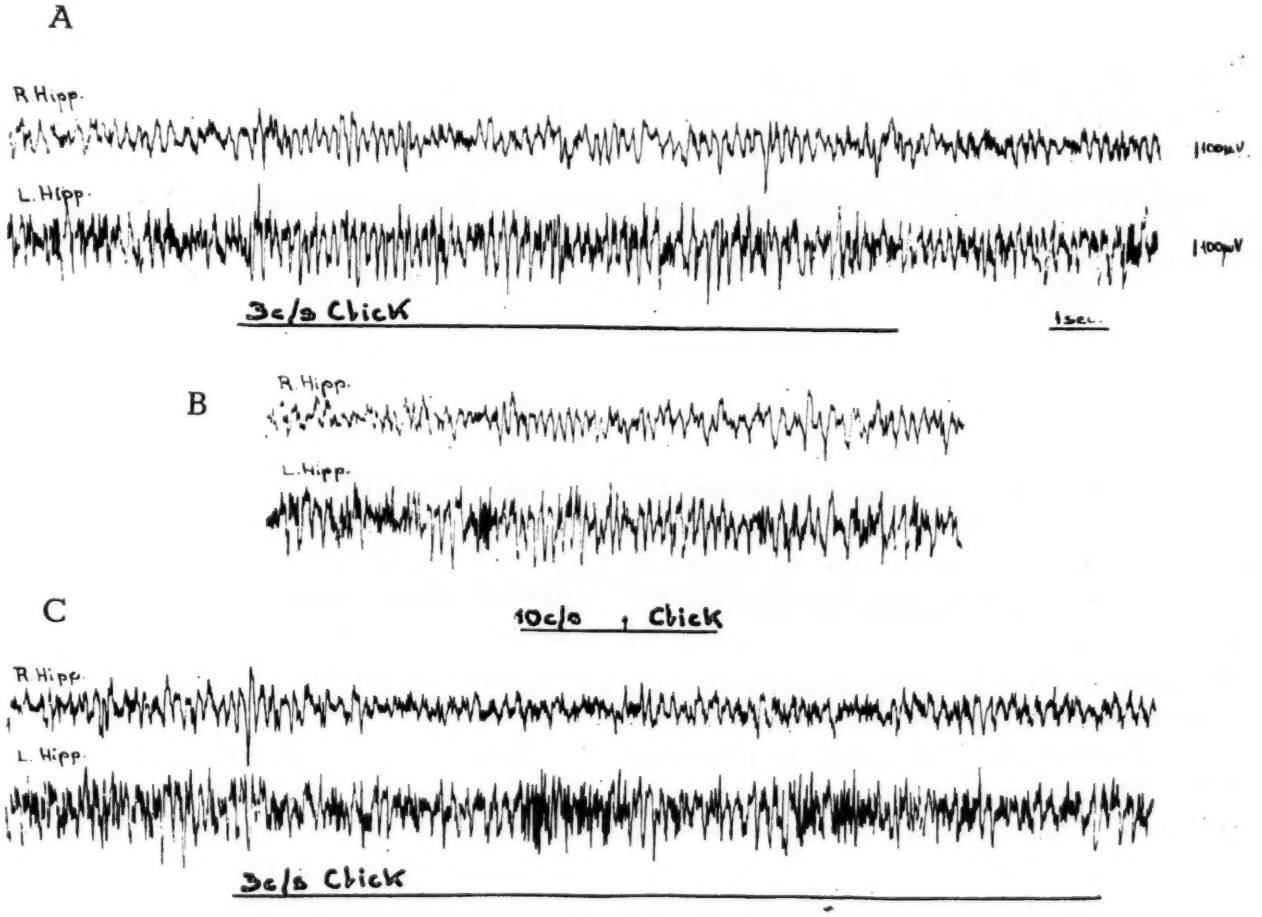


Fig. 5

The same animal as in figure 4 (cat H.28). Changes accompanying the differentiation of the alimentary conditioned reflex.
(Abbreviations and signs as in fig. 4).

A. At its 5th application the negative sound stimulus (3 c/sec. click) elicits the rhythmic slow response.

B. During the elaboration of the differentiation, the effect of the positive conditioned sound stimulus (10 c/sec.) becomes temporarily labile again and elicits the slow potentials and the orientative reflex.

C. When differentiation has been completed, the negative sound desynchronizes hippocampal activity.

At this stage of development of the conditioned reflex the somatic as well as the electrical manifestations still show variations. A change of the experimental situation, external inhibition, lengthening of the interval between the associations will often produce reappearance of the slow response and a pronounced orientative reflex. The lability of the reflex

is indicated by the fact that in each session it is generally the slow response that dominates during the first associations and it is only later that it is supplanted by definite desynchronization. The latency of the conditioned reflex also changes in accordance with the electrical changes. After a longer period of time these changes subside and definite initial desynchronization can be observed again as early as at the first associations in the session.

In addition to finding the desynchronization of hippocampal electrical activity to be a regular phenomenon inseparably associated with the stabilization of the conditioned reflex, in some animals the final form of the electrical changes during the entire period of reaction proved to be more complicated than described above. For instance, in some of the animals it was observed that at the beginning of the stimulus the desynchronization was invariably preceded by a single slow wave (fig. 4 D). It is probable that this is the only remaining component of the earlier slow response without a visible somatic manifestation. In other animals the initial desynchronization seen at the beginning of the movement is again supplanted by a few slow potentials and, then, during and after the conditioned reaction, a new desynchronization can be observed (fig. 6 C). The latter phenomenon was chiefly observed when the animal, while carrying out the conditioned reflex, was not performing the stereotyped movements which it had learned or when the execution of the reflex was complicated intentionally

As has been said the background activity of the hippocampus is complex, fast and slow components taking each others places at irregular intervals. According to our observations every manifestation of the animal is faithfully reflected in the hippocampal activity and, although the experimental situation minimizes spontaneous manifestations, the slow waves observed in the course of development of the conditioned reflex appear also during the intervals between the stimuli. This circumstance made it important to decide how far the activity dominant before the application of the stimulus determined the character of the response. A careful study of this question showed that the electrical responses were not determined by the background activity, but only by the character of the stimulus. When the background activity is desynchronized the stimulus may cause further increasing desynchronization (fig. 4 D) but may also evoke slow waves immediately (fig. 2 A and 3 A). In a similar way, in the background of a slow activity the stimulus may cause desynchronization directly (fig. 6 B) but may also accentuate the slow activity (fig. 6 A and 2 B).

Generally, the hippocampal desynchronization observed during the stabilization of the conditioned reflex is accompanied by desynchronization in the neocortex too. Departure from this was observed in some cases in the activity of the motor cortex, where, occasionally, slow components appeared simultaneously with an initial, marked hippocampal desynchronization (in the form of the so called "en arceau" potentials described by Gastaut in 1952, fig. 7 B). At the time of appearance of these potentials the animal is motionless. At the same time desynchronization may be observed over other regions of the neocortex.

Stage of generalization of the conditioned reflex. At this stage of development of the conditioned reflex, which is characterized by the appearance of the foregoing desynchronization, the conditioned reflex is in a state of sensory generalization, i.e. a great variety of stimuli similar to the conditioned stimulus may elicit the reflex. In connection with this, characteristic manifestations may be observed in the electrical activity of the hippocampus. Those stimuli which formerly elicited slow potentials from the hippocampus, now cause desynchronization and evoke the conditioned reflex.

Differential inhibition. At the beginning of the establishment of differential inhibition the negative sound stimulus elicits a conditioned reflex because of the generalization and causes desynchronization in the hippocampus accordingly. On omitting the reinforcement several times, a pronounced change follows. During the entire period of the negative stim-

ulus the characteristic slow potentials reappear, the animal performs orientative movements; the conditioned reaction, on the other hand, gradually subsides (fig. 5 A). At the same time a change may be observed also in the effect of the positive stimulus; the latency of the conditioned reflex becomes longer, vigorous orientative movements are observed again and, simultaneously, the slow potentials reappear (fig. 5 B).

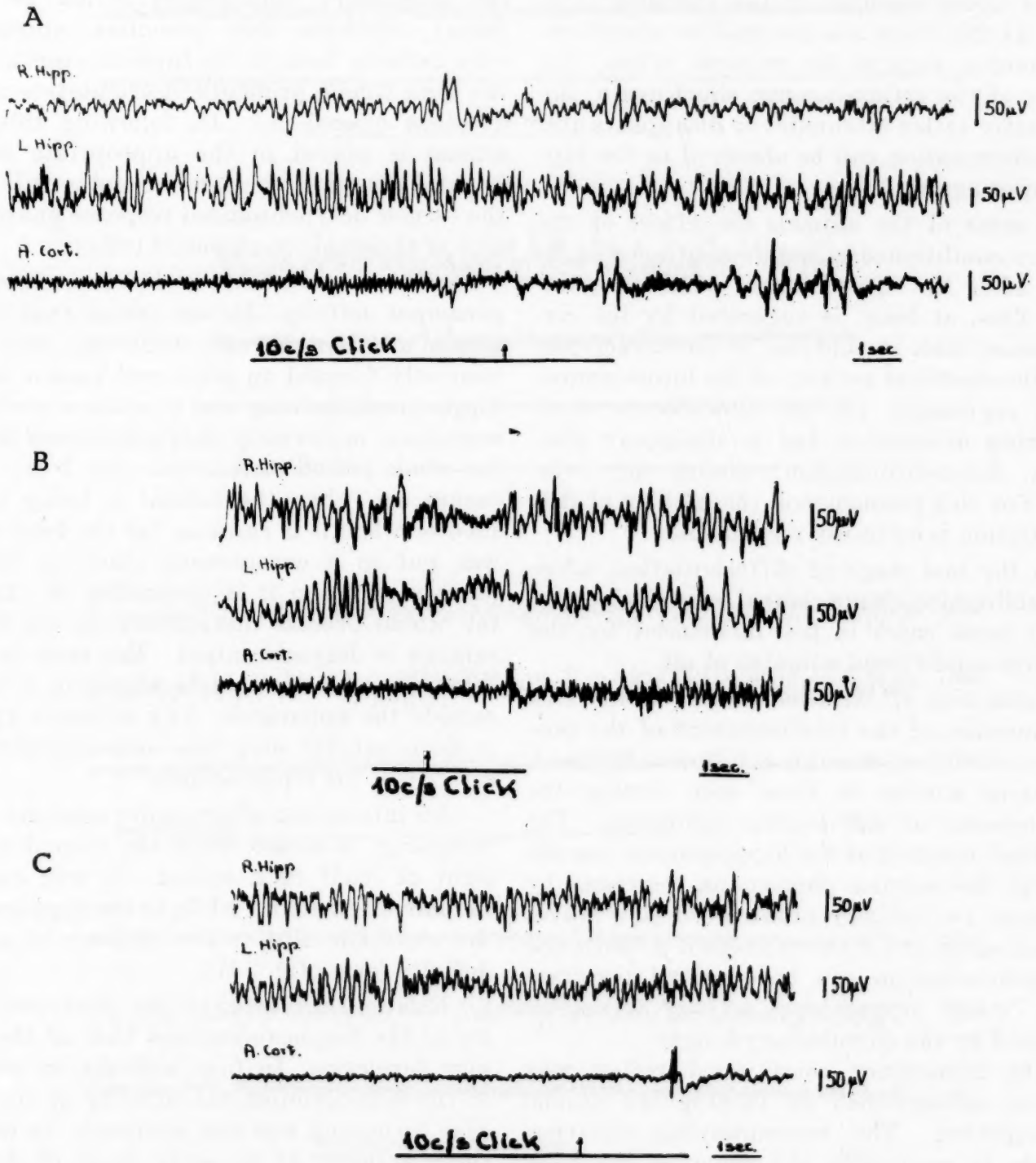


Fig. 6

Cat H.17. An example of the different forms of desynchronization. Alimentary conditioned reflex. Abbreviations: R. Hipp.: Right hippocampus. L. Hipp.: Left hippocampus. A. Cort.: Auditory cortex.

A. The 10 c/sec. click stimulus still elicits a series of slow waves at the first appearance of the conditioned reflex.

B. The effect of the stimulus at the stabilization of the reflex.

C. While performing the reflex, the animal uses movements differing from those learned during conditioning. After initial desynchronization slow waves appear again. The arrow indicates the onset of the motor reaction.

Finally, at the stabilization of the differentiation more or less pronounced desynchronization is seen during the whole period of application of the stimulus (fig. 5 C), slow potentials often appearing in a rebound like manner upon cessation of the stimulus (fig. 7 C). At this stage also the positive conditioned stimulus regains its original effect, the latency of the reflex becomes short again, the orientative reflex attenuates or disappears and desynchronization can be observed in the hippocampus again.

In some of the animals the effect of the positive conditioned stimulus continues to be labile after the establishment of differentiation. This, at least, is suggested by the circumstance that, in contrast to the earlier picture, the electrical activity of the hippocampus shows regression, i.e. the slow waves characterizing orientation fail to disappear altogether, desynchronization remains only relative. For this phenomenon the lability of differentiation is certainly responsible.

In the last stage of differentiation, after its stabilization, hippocampal electrical activity in most cases is not influenced by the negative conditioned stimulus at all.

Extinction of the conditioned reflex. Discontinuation of the reinforcement of the positive conditioned stimulus is followed by manifestations similar to those seen during the development of differential inhibition. The electrical reaction of the hippocampus, together with the somatic phenomena, regresses by one step, i.e. initially pronounced slow waves appear again and if the extinction is continued desynchronization can be observed temporarily; finally hippocampal activity is not influenced by the stimulus any longer.

The alimentary conditioned reflex may also be extinguished by feeding the animal to repletion. The accompanying electrical change is essentially the same as the foregoing: parallel to the satiation of the animal the latency of the reflex increases gradually, and of the conditioned reflex nothing but the orientative reaction is left.

The influence of conditioned stimuli in an inadequate situation. If, after the stabilization of the positive conditioned reflex the conditioned stimulus is applied in an indifferent environment or in one not corresponding to the character of the conditioned stimulus (e.g. a conditioned defensive sound stimulus in the apparatus for the elaboration of the alimentary conditioned reflex or vice versa), rhythmic slow potentials appear in very definite form in the hippocampus and at the same time a pronounced orientative reflex develops (fig. 7 A). If, following this, the animal is placed in the appropriate experimental situation, the same stimulus will elicit the former desynchronized response characteristic of the stable conditioned reflex.

Spontaneous behavioural changes and hippocampal activity. It was found that if the animal's attention was definitely and permanently focused on some well-known object, hippocampal activity was sometimes perfectly, sometimes moderately desynchronized during the whole period of reaction (fig. 7 D). This occurs e.g. when the animal is being shown food or when it is running for the food which was put in a conspicuous place in the apparatus or when it is consuming it. During the whole process the activity of the hippocampus is desynchronized. The same may be seen, when the animal is watching a mouse outside the apparatus. Any stimulus applied in deep natural sleep also desynchronizes the activity of the hippocampus.

An interesting effect, quite opposite to the foregoing, is caused when the animal catches sight of itself in a mirror. It will examine the mirror excitedly while in the hippocampus the rhythmic slow waves appear in a very definite form (fig. 2 B).

Relationship between the electrical activity of the hippocampus and that of the reticular formation. In four animals, in addition to the hippocampus, the activity of the reticular formation was also analysed. In three of these animals, at an early stage of development of the conditioned reflex, the conditioned stimulus or stimuli which had previously elicited the slow potentials, evoked slow waves in the reticular formation of the mesencephalon which were similar to those obtained from the hippocampus (fig. 2 A, 2 B, and 10). The form and frequency of the slow waves was

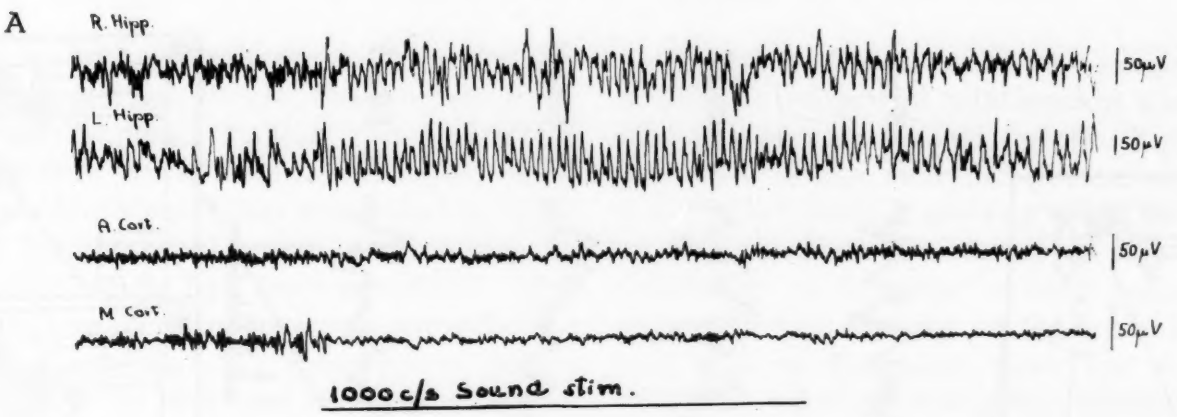


Fig. 7

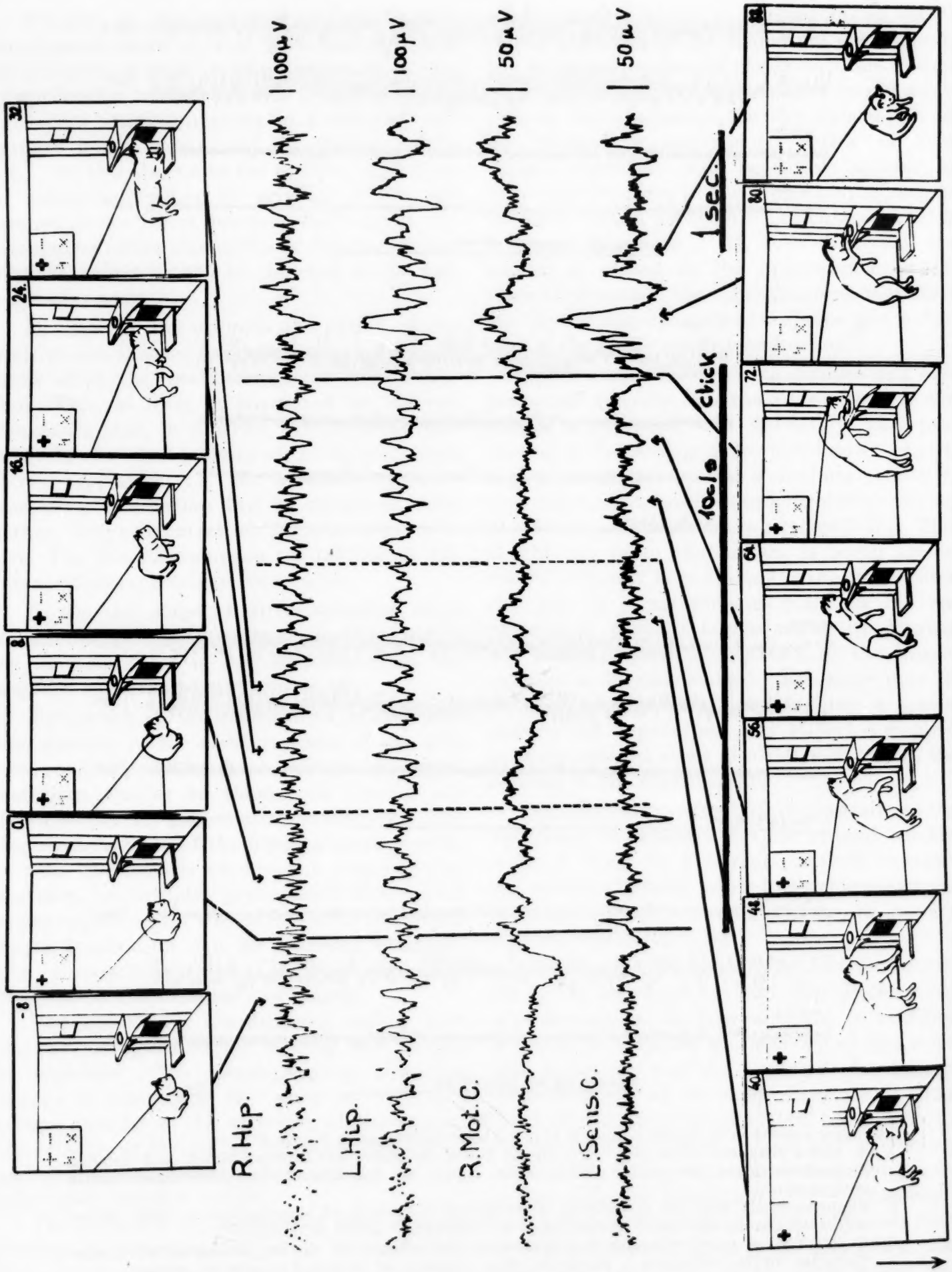
The same animal as in figure 6 (Cat H.17). (Abbreviations as in figure 6).

A. A sound stimulus elaborated as a signal for a defensive conditioned reflex and causing desynchronization as such, evokes slow waves in an alimentary conditioned reflex environment.

B. Simultaneously with the intensively desynchronized periods of hippocampal activity slower waves appear in the motor cortex upon a differential sound stimulus.

C. A differential sound stimulus desynchronizes the activity of the hippocampus, on discontinuation of the stimulus a rhythmic slow response of rebound character appears.

D. During a reaction of spontaneous attention hippocampal activity is chiefly desynchronized. The duration of attention is indicated by the solid line.


100 μV
100 μV
50 μV
50 μV
1 sec.
click
10 c/s
R. Hip.
L. Hip.
R. Mot. C.
L. Sens. C.

identical in both structures; a difference was only seen in the amplitude, those of the reticular formation being smaller. In connection with these slow waves obtained from the reticular formation a suspicion arose that perhaps waves of hippocampal origin, transmitted by volume conduction had been recorded. This possibility however, to be seems excluded by the observations that (1) these waves do not always appear in the two structures at the same time (the hippocampus generally precedes the reticular formation) and (2) when the slow waves disappear from the reticular formation they still persist in the hippocampus. The characteristics of these potentials would seem to suggest, that they are identical with the phenomenon demonstrated in connection with the conditioned reflex in the reticular formation (Yoshii, Pruvot and Gastaut 1957). Our observations seem to indicate that the origin of these waves is, in the first place, the hippocampus. It is also possible, however, that we are dealing with a more general phenomenon of development of the temporary connections which manifests itself also in other structures. (The potentials examined by us are certainly not frequency-specific.)

In one of the animals, on a single occasion, a definite reciprocal relationship was observed also between the activity of the hippocampus and that of the reticular formation. During a period of resting activity when in the reticular formation slow waves of 5 c/sec. were dominant, a familiar calling sound desynchronized the activity of the reticular formation and at the same time the slow waves identical with the foregoing appeared in the hippocampus (fig. 9).

In one of our 4 animals hippocampal slow activity was invariably accompanied by desynchronization in the reticular formation.

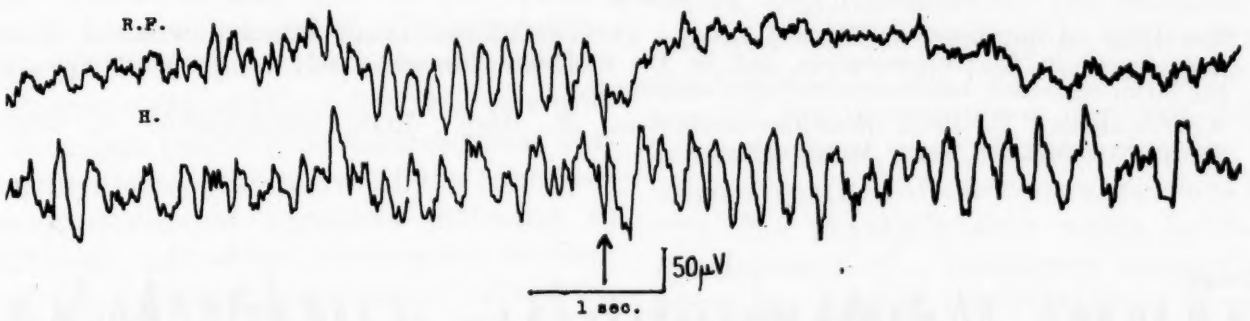


Fig. 9

Cat M.4. Inverse responses in the reticular formation and the hippocampus upon the application of a calling sound stimulus indicated by arrow. For further explanation see text. Abbreviations: R. F.: Reticular formation. H.: Hippocampus.

Correlations between the activities of different hippocampal segments. In order to compare the different segments of the hippocampus, at least two pair of electrodes were implanted in the majority of the animals. If the electrodes were placed in nearly identical segments on both sides, no essential differences except in amplitude were noted in the activity. The electrical changes described in the foregoing chapters — rhythmic slow potentials and desynchronization — were most pronounced in the dorsoanterior (commissural) segment of the hippocampus. An essential dif-

Fig. 8

Cat H.15. Demonstration of the simultaneous appearance of the rhythmic slow response and the orientative reaction. Recordings of the motor reaction (motion pictures) and the electrical activity are obtained synchronously. The motion pictures were taken at a rate of 16 pictures/sec. Every 8th of the pictures was projected and copied graphically. The solid vertical lines indicate the duration of the conditioned stimulus, the dotted vertical lines that of the orientative reaction. The conditioned sound stimulus is also shown by the box flashing the symbol +. The source of the conditioned sound stimulus (loud-speaker) is indicated by a black box under the feeding device, towards which the orientation reflex is directed. As can be seen the rhythmic slow activity and the orientative reaction coincide. Abbreviations: R. Hip.: Right hippocampus. L. Hip.: Left hippocampus. R. Mot. C.: Right motor cortex. L. Sens. C.: Left somato-sensory cortex.

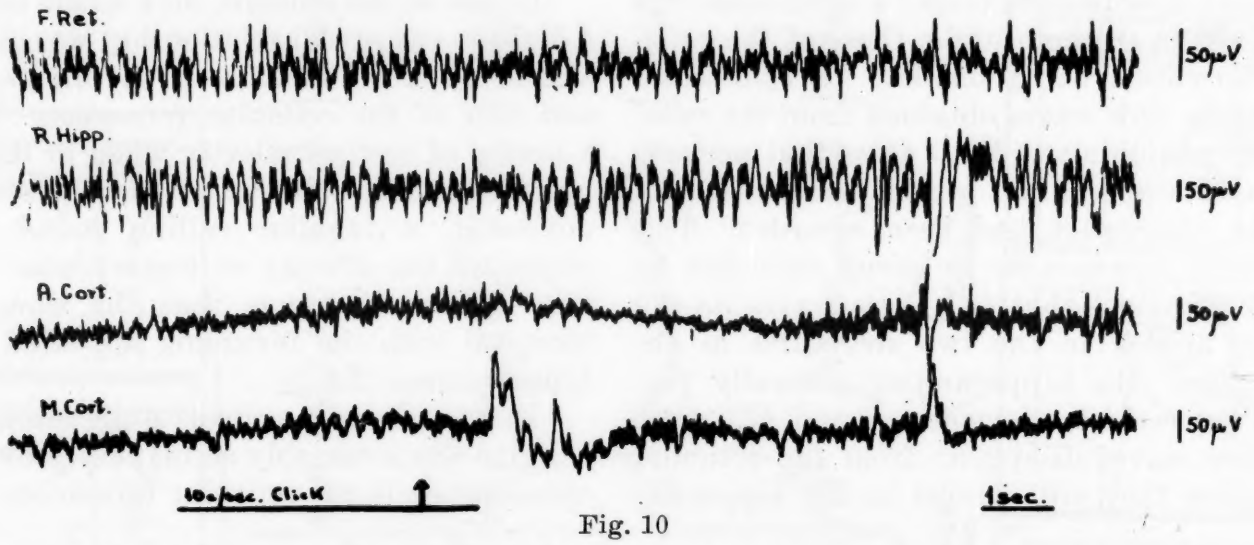
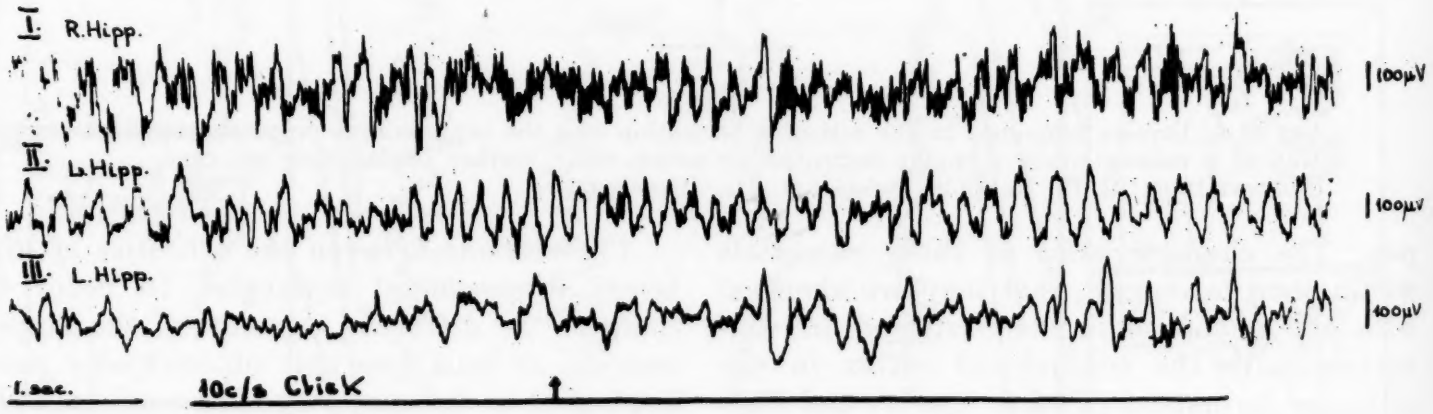


Fig. 10

Cat H.19. Alimentary conditioned reflex. The conditioned sound stimulus evokes 5 c/sec. slow waves in the hippocampus and in the reticular formation of the mesencephalon, in the latter structure, however, with lower amplitude.

Abbreviations: F. Ret.: Reticular formation. R. Hipp.: Right hippocampus. A. Cort.: Auditory cortex. M. Cort.: Motor cortex



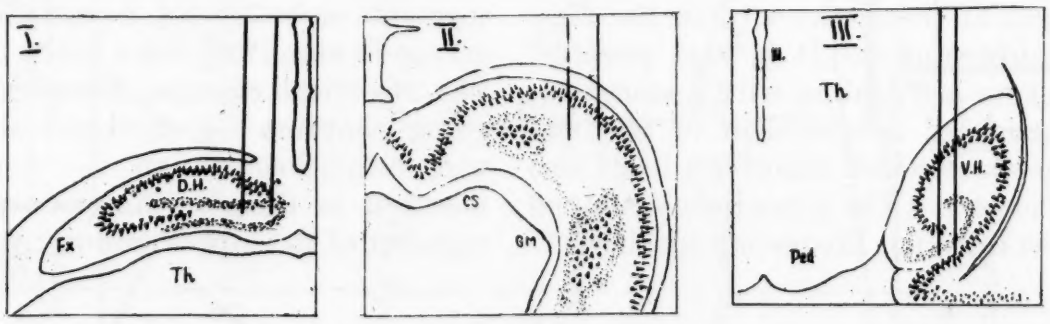


Fig. 11

Cat H.27. An example of the relationship between the activities of three different hippocampal segments during the initial phase of development of the alimentary conditioned reflex. Immediately before or during the motor reaction the 10 c/sec. sound stimulus causes moderate incipient desynchronization in each of the regions; in the right hippocampus (dorso-anterior segment) the desynchronization continues to increase, in the left hippocampus (intermediate segment) marked slow waves appear at the same time. The change in activity of the basal segment is not characteristic. The sites of registration were identified in Nissl preparations.

Abbreviations: R. Hipp.: Right hippocampus. L. Hipp.: Left hippocampus.

ference was observed in the activity of the ventrobasal part of the hippocampus. As has been reported by McLean (1957), the activity of this segment very much resembles that of the neocortex, the majority of stimuli eliciting desynchronization in it (fig. 11). The characteristic slow discharges were either not seen in this region at all or only in irregular, atypical form.

As a spontaneous manifestation in one animal, and in the stage of elaboration of the alimentary conditioned reflex in another, definite reciprocity between two different hippocampal segments (dorso-anterior and intermediate) was invariably seen in the appearance of the slow waves and the desynchronization (fig. 11). We have not been able to find a satisfactory explanation for this phenomenon. It might possibly be assumed that this phenomenon is representative of the functions of two hippocampal segments differing in their afferent connection. During the development of the defensive conditioned reflex the activity of the two examined regions showed identical changes.

As to the origin of the slow waves an attempt was made to draw conclusions chiefly from records taken with monopolar technique. Naturally, this conclusion could only be tentative because of the coarseness of the electrodes. The most characteristic forms of the slow waves were observed with the electrodes placed near the pyramidal cells. Other sites very favorable to the recording of slow waves were the subicular region and the region between the area CA_4 and the subiculum. Although in one of the animals each tip of the electrode was placed in the hippocampus and most certainly not touching another foreign structure the activity was, similary to that of the neocortex, namely fast, and the rhythmic slow waves only appeared in traces. In the same animal the rhythmic slow discharges were easily obtained from another region of the hippocampus.

DISCUSSION

At its first application an entirely unknown stimulus or any stimulus applied in natural deep sleep will desynchronize the activity of the hippocampus. This desynchronization is in essence the same as that of the neocortex: the slow waves disappear, the amplitude decreases in size, the only difference being a more moderate increase in frequency. This initial effect is easy to distinguish from the synchronized response which occurs when association of the indifferent stimulus with some unconditioned reflex function (feeding or a painful stimulus) is begun. The characteristic hippocampal slow waves described by Green and Arduini (1954) appear simultaneously with the appearance of the first somatic signs of the temporary connection and then, at the stabilization of the reflex, desynchronization follows again. Three essential conclusions may be drawn from this statement: (1) The form of arousal or activation of the hippocampus does not differ essentially from that of the neocortex or any other structure of the central nervous system. (2) The rhythmic slow waves indicate the development of a temporary connection. (3) From the marked electrical signs accompanying the development of the temporary connection one may be infer that the hippocampus plays a significant role in the establishment of the temporary connection.

In the course of their investigations with microelectrodes Ricci, Doane and Jasper (1957) have found that the changes taking place in the examined cortical region during desynchronization are by no means uniform in character. However, it is believed that this assertion does not abolish the old empirical fact that, at every level of the central nervous system, desynchronization indicates increased excitation, and slow waves decreased activity or inhibition. According to our present-day knowledge there would be only one surprising exception to this rule, namely the hippocampus. This is all the more astonishing because the difference in structure between the hippocampus and the neocortex is considerably smaller than e.g. that between the neocortex and the basal ganglia. The electrical reactions of the latter, however, do not differ essentially in their extremes, at the height of excitement and at rest. On the basis of this assumption it is thought probable that the hippocampal desynchronization observed by us corresponds

to a similar functional level of the neocortex, i.e. to an activated form of function and the rhythmic slow potentials to the characteristics of relative rest, similarly to the alpha waves of the neocortex. As will be seen later this interpretation of the slow waves makes it possible to reconcile the electrical changes observed during the development of the conditioned reflex with responses obtained by stimulating the hippocampus.

From the data known so far it cannot be established whether the same or different nervous elements are responsible for the two types of hippocampal activity. According to Green and Machne (1955) the groups of rhythmic discharges from certain units are in definite correlation with the slow waves obtained at the same time; other units, however, are quite independent. The coarse bipolar leads used in this experiment have offered little evidence as to the origin of the slow potentials. We have, however, found suggestive evidence that the slow discharges might originate in the pyramidal cells of the hippocampus. The fact that it is only after a certain number of associations and simultaneously with the first manifestations of the development of the temporary connection that the conditioned stimulus begins to elicit the rhythmic slow potentials would seem to indicate beyond any doubt that *the appearance of the rhythmic slow activity indicates the presence of a temporary connection.* It should be pointed out that it was possible to deduce this from the first original description of these potentials. When analyzing the conditions for the elicitation of the slow activity Green and Arduini (1954) established that different stimuli were not equally effective in "arousing" the hippocampus and, what was surprising, it was not the intensity of the stimulus that the effect was proportional to: "The intensity of auditory stimuli seems less important than other factors. The loud sound of the toy cricket, for example, is less effective than a low whistle or hiss." When analyzing the effect of stimuli applied in superficial sleep Rimbaud, Passouant and Cadilhac (1955) made an observation which was similar in essence: "Cette réaction d'éveil avec désynchronisation corticale et synchronisation hippocampique est particulièrement majorée et facilement reproduite lorsque le stimulus a un caractère affectif: miaulement ou aboiement." Both assertions have one feature in common: the stimulus to elicit the slow response must be familiar to the animal, i.e. it has been in conditioned connection with the animal before. However, it is surprising and needs to be explained why this slow activity is elicited by such a great variety of stimuli and why it is so often present in the resting activity of the hippocampus. On the basis of our experience the following explanation might be offered. The slow activity of the hippocampus indicates an initial and labile form of the temporary connection. Such connections are certainly established in large numbers in the natural conditions of the animal's life. (As can be seen from our experiments, the slow potentials often appear as soon as after a few associations of the conditioned stimuli. Furthermore, it may be deduced from our observations, that a relatively slight change in the experimental environment will suffice to cause the conditioned reflex to regress to such a labile form.) At any rate, the appearance of the slow waves in the hippocampus indicates that the stimulus, in some form or other, has been in connection with the animal before. The basic feature of the temporary connection indicated by the slow response consists in its labile and nonspecific nature. At this stage of development of the reflex the stimulus has acquired some significance to the animal (which finds expression in the orientative reaction), its precise meaning, however, is yet uncertain. Using everyday language to explain this, one might say that the animal has come to realize that the stimulus means something, however, it does not know what. This labile, not strictly defined feature is common to all stimuli that elicit the slow response from the hippocampus. That is why a familiar calling sound (e.g. "puss") or imitation of meaowing evokes slow waves. The same process finds expression also in the mirror effect. The image reflected in the mirror is familiar to the animal and yet the lack of some natural elements will

render the impression vague. As soon as the meaning of the stimulus has been made definite, the slow potentials cease and are replaced by desynchronization. Based on the foregoing it may be said that *the inverse electrical activities of the hippocampus and the neocortex represent different functional states of the two structures rather than a difference in reactivity or in the form of activation.*

It is difficult to account for the considerable difference in rhythmic slow activity of the hippocampus seen in different species. In the rabbit these waves seem to be permanently present, also in the resting activity, or are easy to elicit. In the cat, but chiefly in the monkey, they are considerably rarer and less characteristic (Green and Arduini 1954). It would hardly be justifiable to make the structural characteristics of the hippocampus responsible for this difference. On the basis of our experience it would seem a plausible explanation that this difference expresses various relations between the differentiated and nondifferentiated temporary connections at various levels of the phylogenetic scale.

The acceptance of the notion that hippocampal slow activity is an indication of the development of a temporary connection suggests an interesting but at first surprising interpretation of the orientative reaction. Namely, if hippocampal slow activity is an early sign of a temporary connection the orientative reflex, which is an invariable concomitant of slow activity, must represent a conditioned reflex phenomenon too. This conclusion is surprising because it is generally accepted that the orientative reaction belongs to the group of unconditioned reflexes.

In view of its mechanism it is not impossible that the orientative reflex has two separate forms. Also, in the course of these experiments, reactions consisting of short phasic movements of the head, not accompanied by slow potentials were in some cases observed on the application of unknown stimuli. The electrical as well as the somatic characteristics of this phasic reaction are easily separated from those which only appear in the course of development of the conditioned reflex, and consist of tonic orientative (searching) movements. Thus it is not impossible that the above-mentioned phasic reaction represents the inborn, unconditioned form of the orientative reflex.

One may add that the notion of the orientative reflex as representing an acquired, conditioned reflex phenomenon is not quite foreign to the conditioned reflex theory. This is indicated by some features common to the orientative as well as to the conditioned reflex, e.g. the long established facts that the orientative reflex, like a conditioned reflex and unlike an unconditioned reflex, can be extinguished, furthermore that the orientative reflex may be elaborated as a true conditioned reflex (Ivanov-Smolenski 1927). Similar supporting evidence may be obtained from investigations into the ontogenetic evolution of the orientative reflex (Trosihin 1953).

From the electrical manifestations accompanying the establishment of the conditioned reflex one may positively conclude that at least the tonic form of the orientative reflex described above certainly represents a conditioned reflex phenomenon, and also that this reaction is an organic and peculiar transitional form of development of the temporary connection. It was on the basis of this reasoning that we came to apply the term ''effector generalisation'' to this initial stage of development of the conditioned reflex.

The early electrical signs observed in connection with the development of the conditioned reflex doubtlessly indicate that, in some way or other, the hippocampus plays a fundamental role in the establishment of the temporary connection. This is also confirmed by earlier clinical experience supported by a more recent neurosurgical observation that after lesions of the hippocampus or the mammillary body, impairment or the ability to learn, in more severe cases even complete loss of this function, may be observed in man. (Camper 1928, 1929; Környei and Saethre 1937; Grünthal 1939, 1947; Benedek and Juba 1940, 1941; Konrad and Ule 1951; Ule 1951; Scoville and Milner 1957).

However, by what mechanisms the hippocampus is involved in this function cannot be deduced from the loss of function itself or

from the foregoing electrical changes. Further data are required for the elucidation of this question.

The most invariable somatic concomitant of the rhythmic slow potentials of the hippocampus is the tonic orientative reflex. If it may be assumed that the synchronized activity of the hippocampus, as a peculiar excitatory activity, is responsible for this manifestation then it is justifiable to expect, that electrical stimulation of the hippocampus will elicit similar phenomena. Since stimulation of the hippocampus often causes a contralateral adversion of the head, the question may be raised whether this effect should not be regarded as an elementary component of the physiologic orientative reflex. This, however, is rendered improbably by an earlier observation of ours that manifestations identical with the natural orientative reflex can be elicited by stimulation of the reticular formation or the hypothalamus (Grastyán, Lissák, Kékesi 1956); on the other hand, stimulation of the hippocampus, as will be shown below, inhibits the natural orientative reaction. (It is remarkable that stimulation of the reticular formation and hypothalamus will evoke from the hippocampus the characteristic rhythmic slow waves most easily (Green and Arduini 1954)). Therefore it would seem justifiable to assume that the earliest manifestation of the temporary connection (the tonic form of the orientative reflex) is built up in the reticular formation and the hypothalamus rather than in the hippocampus.

According to the majority of authors, hippocampal stimulation will produce inhibitory phenomena (Hunter and Jasper 1949; Kaada and Jasper 1952, ''arrest reaction''; Cadilhac 1955, ''catalepsy''; McLean *et al.* 1955-56, ''inhibition of conditioned defensive reflex''). Our own experimental findings are in good agreement with these observations: at every level of function inhibitory effects were encountered. Stimulation inhibited movements elicited from the motor cortex, reflexly induced movements, and in the unrestrained animal, the orientative reflex, and the alimentary and defensive conditioned reflexes (Grastyán *et al.* 1956b, 1958). Thus hippocampal stimulation inhibits, among others, the most pronounced reaction which accompanies the hippocampal slow waves, the orientative reflex. It follows, therefore, *that the rhythmic slow waves do not represent increased excitation but,* rather, — as has been pointed out on the basis of other reasoning — *an inhibited state of the hippocampus.*

At the stabilization of the conditioned reflex the orientative reflex gradually disappears and, at the same time, hippocampal activity is desynchronized. This leads to the quite obvious conclusion that *hippocampal desynchronisation* — as a sign of increased excitation — *should be regarded as being responsible for the inhibition of the orientative reflex.*

The inhibition of the orientative reflex is an indispensable condition of the transition of diffuse movements into a special motor reaction. From a psychological aspect the same mechanism could possibly be identified with attention. That the hippocampus plays an active role in this process is also confirmed by our recent observation that hippocampal activity is desynchronised during the spontaneous focusing of attention. In view of the wellknown importance of attention in the process of learning it would seem probable that an impairment of learning ability following hippocampal lesion is due to disturbances in the mechanism of attention (hippocampal inhibition).

The correctness of our assumption depends, of course, chiefly upon whether or not the inhibition elicited from the hippocampus by electrical stimulation really represents a physiological function. A number of observations indicate that it does. We have found that hippocampal stimulation in deep natural sleep does not interfere with sleep (Lissák *et al.* 1957), which, in the Pavlovian sense, corresponds to a generalized inhibition.

Another observation made in the course of these experiments would also seem to suggest an inhibitory role of the hippocampus, i.e. the so called ''en arceau'' potential, described in man (Gastaut 1952), was often seen to appear during desynchronized hippocampal activity; when this potential is checked with

a conditioned reflex method it prooves to be an inhibitory manifestation (Grastyán, Hori, Roger 1957). Further support is given to this inhibitory role by Adey, Segundo and Livingston (1957) who report that hippocampal stimulation inhibits the conduction of impulses from the reticular formation to the diencephalon.

From the character of the rebound reactions following hippocampal stimulation the same conclusion may be drawn. Whatever function we were examining in connection with the hippocampus, rebound reactions were always found to be an invariable manifestation. Rebound facilitation follows the inhibition of movements elicited from the motor cortex or induced reflexly. In conditioned reflex experiments the discontinuation of stimulation of the hippocampus is often followed by activation of the inhibited conditioned reflex (Grastyán *et al.* 1956b, 1958). On the other hand, this complex activating effect may be elicited directly by stimulating the reticular formation and/or the hypothalamus (Grastyán, Lissák, Kékesi 1956). The arousal following the cessation of stimulation applied in natural sleep is also a rebound reaction for which, in all probability, the reticular formation is again responsible (Lissák *et al.* 1957). In the present experiments it was found that on cessation of a negative sound stimulus the desynchronization seen during differential inhibition was followed by a series of rhythmic slow potentials of rebound character. (As has been mentioned these potentials are most readily elicited by direct stimulation of the reticular formation or the hypothalamus.) It is probable that the enhanced pleasure and grooming reactions and vocalization following hippocampal after-discharges, described by McLean (1957), represent similar rebound reactions.

All the foregoing facts unequivocally suggest that the main site of action of the hippocampal inhibitory function is the reticular formation and the hypothalamus. The rebound reaction is an expression of a release of some of the structures in question.

A summing up of the above facts leads to the conclusion that a mutual controlling relationship must exist between the ascending activating system and the hippocampus. Most recently Hugelin and Bonvallet's (1957) studies have drawn attention to a very important inhibitory mechanism of diffuse neocortical origin. Whether the hippocampal inhibition examined by us and the foregoing negative feed-back mechanism have anything in common cannot be decided now, because of the difference in experimental conditions.

The neocortex is capable of influencing the activity of the reticular formation also in a facilitatory manner. This accounts for the fact that arousal may be elicited by the stimulation of certain cortical areas. In contrast to this, we have seen in our experiments that hippocampal stimulation will only have inhibitory effects on functions of the activating system. Viewed from this aspect it would seem probable that the hippocampus plays a leading role in the control of the activating system.

At the present moment it would be difficult to answer the question whether the above-described inhibitory mechanism represents the only physiological function of the hippocampus. In recent years it has been definitely demonstrated that the hippocampus is not representative of olfactory function. However, the gap left by this negative statement has not yet been filled by any other special physiological function. This fact in itself would seem to confirm the view, first advanced by Herrick (1933), that the hippocampus does not perform a special, but rather a general regulatory function. In the behaviour of the animal, and probably at the highest functional level of the activating system, this inhibition manifests itself in controlling the orientation reflex. The fact that the orientation reflex represents an indispensable link in the temporary connection makes this inhibitory function of the hippocampus one of the most important features in the dynamics of higher nervous function — a role which is not out of proportion to the absolute or relative size of this structure.

SUMMARY

The changes in hippocampal electrical activity during the development of alimentary and defensive conditioned reflexes have been examined.

Neocortical desynchronization being accompanied by rhythmic slow potentials in the hippocampus, several authors claim an inverse relationship between the activation of the hippocampus and that of the neocortex. In contrast to this, it was found in the present experiments that at their first applications entirely unknown and indifferent stimuli produced desynchronization in the hippocampus and the rhythmic slow potentials only appeared after a sufficient number of associations of the stimuli i.e. at an early stage of development of the temporary connection. Thus the slow activity of the hippocampus represents a conditioned reflex manifestation.

At the stabilization of the conditioned reflex and simultaneously with the subsidence of the orientative reflex, the slow waves cease again and desynchronization appears. However, the rhythmic slow waves may reappear in association with the orientative reflex, whenever the conditioned reflex becomes labile, or regresses (e.g. at the beginning of development of the differential inhibition, or at extinction).

The observed electrical changes and other data on hippocampal activity suggest that, similarly to the neocortex, desynchronization in the hippocampus is an expression of enhanced activity, and the rhythmic slow waves that of an inhibitory state. Accordingly, the conclusion is advanced that the hippocampus plays an essential role in the inhibition of the orientative reflex and in the stabilization of the temporary connection. This would explain the role of hippocampal lesions in the development of Korsakoff's syndrome.

RÉSUMÉ

On a étudié les changements de l'activité électrique de l'hippocampe pendant l'élaboration des réflexes conditionnés alimentaires et défensifs chez le chat.

Selon plusieurs auteurs il y aurait une relation inverse entre l'activation de l'hippocampe et celle du néocortex, c'est-à-dire la désynchronisation néocorticale serait accompagnée par l'apparition d'ondes lentes rythmiques dans l'hippocampe. Au contraire nous avons établi que les signaux nouveaux et neutres, à leur première application, provoquent une désynchronisation de l'activité hippocampique et les ondes lentes rythmiques ne paraissent qu'après un certain nombre de combinaisons de signaux, c'est à dire dans le stade précoce du développement de la liaison temporaire. L'activité lente de l'hippocampe est donc une manifestation électrique correspondant à un réflexe conditionné. Au moment de la stabilisation du réflexe conditionné, simultanément avec la disparition du réflexe d'orientation, les ondes lentes disparaissent de nouveau et sont remplacés par une désynchronisation du tracé. Mais les ondes lentes rythmiques — accompagnées du réflexe d'orientation — peuvent reparaître, quand le réflexe devient labile, ou est en régression (au commencement de la différentiation, ou à l'extinction).

Basé sur les changements électriques exposés et des données d'autre nature relatives au fonctionnement de l'hippocampe on suppose que dans l'hippocampe — comme dans le néocortex — la désynchronisation correspond à un état d'excitation plus élevé et les ondes lentes rythmiques à un état inhibé. Il semble donc que l'hippocampe joue un rôle fondamental dans l'inhibition du réflexe d'orientation et ainsi dans la stabilisation du réflexe conditionné. Cette constatation permet de développer une explication tentative du rôle joué par la lésion de l'hippocampe dans la production du syndrôme de Korsakoff.

ZUSAMMENFASSUNG

Es wurden die "Änderungen in der Tätigkeit des Hippocampus während der Entwicklung von bedingten Nahrungs und Abwehrreflexen bei der Katze untersucht.

Da die neokortikale Desynchronisation von rhythmischen langsamen Potentialen im Hippocampus begleitet wird, behaupten mehrere Autoren, dass zwischen der Aktivierung des Hippocampus und des Neocortex ein umgekehrtes Verhältnis besteht. Im Gegensatz

hierzu wurde in den gegenwärtigen Versuchen festgestellt, dass vollkommen unbekannte und indifferente Reize bei ihrer ersten Anwendung im Hippocampus Desynchronisation verursachen und die rhythmischen langsamen Potentiale nur nach einer entsprechenden Zahl von Assoziationen der Reize, d.h. im Frühstadium der Entwicklung des bedingten Reflexes, erscheinen. Demnach stellt die langsame Aktivität des Hippocampus eine Manifestation in der Art eines bedingten Reflexes dar. Zur Zeit der Stabilisierung des bedingten Reflexes und gleichzeitig mit dem Abklingen des Orientierungsreflexes hören die langsamen Wellen wieder auf und es tritt Desynchronisation in Erscheinung. Die rhythmischen langsamen Wellen können aber in Verbindung mit dem Orientierungsreflex wieder erscheinen, immer dann wenn der bedingte Reflex labil wird, oder sich zurückbildet (z. B. am Anfang der Entwicklung der Differenzierungshemmung, bei der Auslöschung).

Aus den beobachteten elektrischen Veränderungen und aus anderen Angaben über die Tätigkeit des Hippocampus geht hervor, dass die Desynchronisation im Hippocampus wie im Neokortex der Ausdruck einer gesteigerten Tätigkeit ist und dass die rhythmischen, langsamen Wellen einen Hemmungszustand anzeigen. Dementsprechend ist der Schluss erlaubt, dass der Hippocampus in der Hemmung des Orientierungsreflexes und in der Stabilisierung des bedingten Reflexes eine wesentliche Rolle spielt. Dies würde auch die Rolle der Ammonshornläsionen in der Entwicklung des Korsakowschen Syndroms erklären.

REFERENCES

Adey, W. R., Segundo, J. P. and Livingston, R. B. Corticifugal influences on intrinsic brain-stem conduction in cat and monkey. *J. Neurophysiol.*, **1957**, *20*: 1-16.

Benedek, L. und Juba, A. Korsakowsyndrom, Störungen der zentral-vegetativen Regulation und Hypothalamus. *Arch. Psychiatr.*, **1940**, *111*: 341-372.

Benedek, L. und Juba, A. Weitere Beiträge zur Frage des anatomischen Substrates des Korsakowschen Symptomenkomplexes. *Arch. Psychiatr.*, **1941**, *112*: 505-516.

Cadilhac, J. *Hippocampe et épilepsie: A propos d'une série d'expériences sur le cobaye et le chat et de l'exploration électrique de la corne d'Ammon chez l'homme.* Montpellier, Paul Déhan, **1955**.

Conrad, K. und Ule, G. Ein Fall von Korsakow-Psychose mit anatomischem Befund und Klinischen Betrachtungen. *Dtsch. Z. Nervenheilk.*, **1951**, *165*: 430-445.

Gamper, E. Zur Frage der Polioencephalitis haemorrhagica des chronischen Alkoholiker. Anatomische Befunde beim alkoholischen Korsakow und ihre Beziehungen zum klinischen Bild. *Dtsch. Z. Nervenheilk.*, **1928**, *102*: 122-126.

Gamper, E. Schlaf, Delirium tremens, Korsakow'sches Syndrom. *Arch. Psychiatr.*, **1929**, *86*: 294-301.

Gastaut, H. Etude électrocorticographique de la réactivité des rythmes rolandiques. *Rev. Neurol.*, **1952**, *87*: 176-182.

Grastyán, E., Lissák, K. and Kékesi, F. Facilitation and inhibition of conditioned alimentary and defensive reflexes by stimulation of the hypothalamus and reticular formation. *Acta Physiol. Hung.*, **1956**a, *9*: 133-151.

Grastyán, E., Lissák, K., Szabó, J. und Vereby Gy. Uber die functionelle Bedeutung des Hippocampus, In the *Problems of the modern physiology of the nervous and muscle system''*. In honor of Beritashvili. Academy of Sciences of the Georgian SSR. Tbilisi, **1956**b, pp. 67-80.

Grastyán, E., Hori, Y. et Roger, A. Etude electroencéphalographique temporo-spatiale d'un conditionnement moteur chez le chat. Premier Congrès International des Sciences Neurologiques Bruxelles. Les Editions ''Acta Medica Belgica'', **1957**, pp. 464-465.

Grastyán, E., Lissák, K., Kékesi, F., Szabó, J. und Vereby, Gy. Beiträge zur Physiologie des Hippocampus. *Physiologia Bohemoslovenica*, **1958**, *7*: 9-18.

Green, J. D. and Arduini, A. A. Hippocampal electrical activity in arousal. *J. Neurophysiol.*, **1954**, *17*: 533-557.

Green, J. D. and Machne, X. Unit activity of rabbit hippocampus. *Amer. J. Physiol.*, **1955**, *181*: 219-24.

Grünthal, E. Uber das Corpus Mammillare und den Korsakow'schen Symptomenkomplex, *Confinia Neurol.*, **1939**, *2*: 64-95.

Grünthal, E. Uber das klinische Bild nach umschriebenem beiderseitigem Ausfall der Ammonshornrinde. Ein Beitrag zur Kenntnis der Function des Ammonshornes. *Mschr. Psychiatr.*, **1947**, *113*: 1-16.

Herrick, C. J. The functions of the olfactory parts of the cerebral cortex. *Proc. Nat. Acad. Sc.*, **1933**, *19*: 7-14.

Hugelin, A. et Bonvallet, M. Tonus cortical et contrôle de la facilitation motrice d'origine réticulaire. *J. Physiol.*, **1957**, *49*: 1171-1200.

Hugelin, A. et Bonvallet, M. Etude expérimentale des interrelations réticulo-corticales; proposition d'une théorie de l'asservissement réticulaire à un système diffus cortical. *J. Physiol.*, **1957**, *49*: 1201-1023.

Hugelin, A. et Bonvallet, M. Analyse des postdécharges réticulaires et corticales engendrées par des stimulations électriques réticulaires. *J. Physiol.*, **1957**, *49*: 1225-1234.

Hunter, J. and Jasper, H. H. Effects of thalamic stimulation in unanaesthetized animals. *EEG Clin. Neurophysiol.*, **1949**, *1*: 305-324.

Ivanov-Smolenskij, A. G. *Russk. Phys. Journ.*, **1927**, *10*: 257. Cited from Trosihin, V. A. *Phys. Journ.*, SSSR., **1953**, *39*: 265-274.

JOSHII, N., PRUVOT, P. and GASTAUT, H. Electrographic activity of the mesencephalic reticular formation during conditioning in the cat. *EEG Clin. Neurophysiol.*, **1957**, *9*: 595-608.

JUNG, R. und KORNMÜLLER, A. E. Eine Methodik der Ableitung lokalisierter Potentialschwankungen aus subcorticalen Hirngebieten. *Arch. f. Psychiatr.*, **1939**, *109*: 1-30.

KAADA, B. R. and JASPER, H. H. Respiratory responses to stimulation of temporal pole, insula and hippocampal and limbic gyri in man. *Arch. Neurol. Psychiat.*, Chicago, **1952**, *68*: 609-619.

KÖRNYEI, ST. und SAETHRE, H. Die Hypothalamische Localisation der Histologischen Befunde in Korsakow-Fällen. *Acta Psychiatr. Neurol.*, **1937**, *12*: 491-498.

LIBERSON, W. T. and AKERT, K. Hippocampal seizure states in guinea pig. *EEG Clin. Neurophysiol.*, **1955**, *7*: 211-222.

LIBERSON, W. T. and CADILHAC, J. G. Electroshock and rhinencephalic seizure states. *Confinia neurol.*, **1953**, *13*: 278-286.

LISSÁK, K., GRASTYÁN, E., CSANAKY, A., KÉKESI, F. and VEREBY, GY. A study of hippocampal function in the waking and sleeping animal with chronically implanted electrodes. *Acta Physiol. Pharmacol. Neerl.*, **1957**, *6*: 451-459.

MACLEAN, P. D., FLANIGAN, S., FLYNN, J. P., KIM, C. and STEVENS, J. R. Hippocampal function: tentative correlations of conditioning, EEG, drug, and radioautographic studies. *Yale J. Biol. Med.*, **1955-56**, *28*: 380-395.

MACLEAN, P. D. Chemical and electrical stimulation of hippocampus in unrestrained animals. *Arch. Neurol. Psychiat.*, Chicago, **1957**, *78*: 113-142.

RICCI, G., DOANE, B. and JASPER, H. H. Microelectrode studies of conditioning: technique and preliminary results. Premier Congrès International des Sciences Neurologiques, Les Editions "Acta Medica Belgica", **1957**, pp. 401-415.

RIMBAUD, L., PASSOUANT, P. et CADILHAC, J. Participation de l'hippocampe à la régulation des états de veille et de sommeil. *Rev. Neurol.*, **1955**, *93*: 303-308.

SCOVILLE, W. B. and MILNER, B. Loss of recent memory after bilateral hippocampal lesions. *J. Neurol. Neurosurg. Psychiat.*, **1957**, *20*: 11-21.

TROSIHIN, V. A. Razvitije Orientirovochnoj reakcii i stanovlenie dvigatelnih uslovno-oboronitelnih reflexov u schenat. (Development of the orientation and conditioned defensive motor reflexes in the puppy). *Phys. Journ.*, SSSR., **1953**, *39*: 265-274.

ULE, G. Korsakow-Psychose nach doppelseitiger Ammonhornzerstörung mit transneuronaler Degeneration der Corpora mammillaria. *Dtsch. Z. Nervenheilk.*, **1951**, *165*: 446-456.

Reference: GRASTYÁN, E., LISSÁK, K., MADARÁSZ, I. and DONHOFFER, H. Hippocampal electrical activity during the development of conditioned reflexes. *EEG Clin. Neurophysiol.*, **1959**, *11*: 409-430.

PRINTED IN GREAT BRITAIN

HIPPOCAMPAL AND NEOCORTICAL ACTIVITY IN DIFFERENT EXPERIMENTAL CONDITIONS [1]

T. Tokizane, M.D., M. Kawakami, M.D. and E. Gellhorn, M.D.
Laboratory of Neurophysiology, Department of Physiology, Minneapolis, Minn.

(Received for publication: July 2, 1958)

This study grew out of earlier observations (Tokizane, Kawakami and Gellhorn 1957) in which the effect on cortical and subcortical structures of stimulation of the caudate nucleus was investigated in different states of activity of the hypothalamus and the reticular formation. It seemed desirable to extend this work to a study of the behavior of the potentials of the hippocampus under these conditions since: 1, neocortex and hippocampus show fundamentally different reactions in their electrical activities on arousal (Cadilhac 1955; Green and Arduini 1954; Green and Machne 1955; Liberson and Akert 1955; Rimbaud, Passouant and Cadilhac 1955); 2, stimulation of the caudate nucleus induces spindle formation as well as asynchrony (arousal) in the neocortex. In addition, an attempt was made to determine whether the increased synchrony of hippocampal potentials is the expression of an excitatory or inhibitory process.

METHODS

Fifteen cats, prepared under ether and local anesthesia and artificially ventilated, were studied several hours later under Intocostrin or Flaxedil. After craniotomy, cortical potentials were recorded with bipolar silver electrodes (diameter 1 mm.) whereas for the hippocampus and the caudate nucleus concentric needle electrodes (gauge 24) provided with a steel core insulated except for 0.5 mm. at the tip were used. The subcortical electrodes were inserted by means of the Horsley-Clarke apparatus. A 6-channel Grass electroencephalograph served for the recording of the potentials, and a square wave pulse generator (Arthur H. Thomas) in conjunction with Schmitt's isolation unit was used for stimulation of the caudate nucleus and afferent nerves. In two cats the Offner frequency analyser (type 830) was applied for a more detailed study of the hippocampal potentials.[2] The locations of the tip of the subcortical electrodes were identified histologically.

RESULTS

1. *The hippocampal electrogram of the cat at rest and in spontaneous and induced arousal.*

The pattern of the hippocampal electrogram of the unstimulated cat was variable. Seven cats showed a resting activity of the hippocampus similar to that described by Green *et al.* (1954) for the rabbit. While a sleep pattern prevailed in the neocortex, the electrogram of the hippocampus showed slow and fast waves mixed irregularly. Spontaneous cortical arousal (asynchrony) was accompanied in the hippocampal electrogram by a train of regular sinusoidal waves on which fast potentials of low amplitude were superimposed. The frequency of the slow and fast waves of the hippocampus seemingly underwent characteristic changes on arousal. The frequency of the slow potentials increased from 2-3/sec. to 3 to 4/sec. Of the fast potentials which were most conspicuous in the 10-14 and 20-25/sec. range at rest, the 10-14/sec. group was markedly diminished during arousal, while the 20-25/sec. group seemed unchanged.

In 8 cats the hippocampus showed chiefly fast waves and a few slow waves in spite of marked arousal in the ECG. In these cats the effect of afferent stimulation was nil

[1] These studies were aided by a grant from the Louis W. and Maud Hill Family Foundation.

[2] See Nakao, Ballin and Gellhorn (1956) for further details.

although CO_2 (see below) still exerted a slight characteristic effect.

In some instances the hippocampal electrogram was dominated by 40/sec. potentials of large amplitude suggesting that mechanical irritation through the hippocampal electrode had caused a hippocampal seizure.

Figure 1 illustrates the effects of spontaneous arousal. The effects on the suprasylvian gyrus and the hippocampus seem to be diametrically opposed. Whereas the cortical potentials were greatly increased in frequency and decreased in amplitude, the hippocampal electrogram was characterized by a regularization of slow waves of increased amplitude.

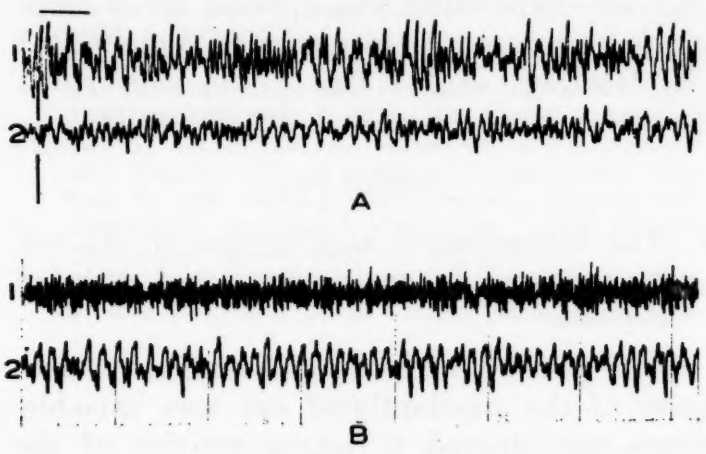


Fig. 1
Neocortex and hippocampus in spontaneous arousal. A. Resting activity; B. spontaneous arousal; (1) L. middle suprasylvian gyrus; (2) L. hippocampus. Calibration in figures 1-6, 1 sec. and 100 μV.

Similar effects were seen on afferent stimulation. Mechanical stimulation of the skin (stroking the back), auditory (click) and nociceptive stimuli (immersion of the tip of the tail in water of 55-75°C) served for this purpose. These stimuli were particularly effective when they were applied during a resting state characterized by synchronous discharges in the neocortex and irregular slow and fast activity in the hippocampus. In the alert cat, however, even a strong stimulus caused little or no changes in the hippocampus. In contrast to earlier observations on the rabbit (Green and Arduini 1954) the arousal pattern appeared almost immediately in the neocortex but developed with some delay in the hippocampus.

Figure 2 illustrates the fact that the typical arousal patterns are elicitable on stimulation of visceral nerves (splanchnics and vagi). Attention is called to the fact, illustrated in figure 2A, that the slow waves from the hippocampus which appeared on stimulation showed a gradual increase in amplitude which persisted for some time in the post-stimulatory period. In addition, table I shows that the frequency of the slow hippocampal waves increases with the intensity of the afferent stimulation.

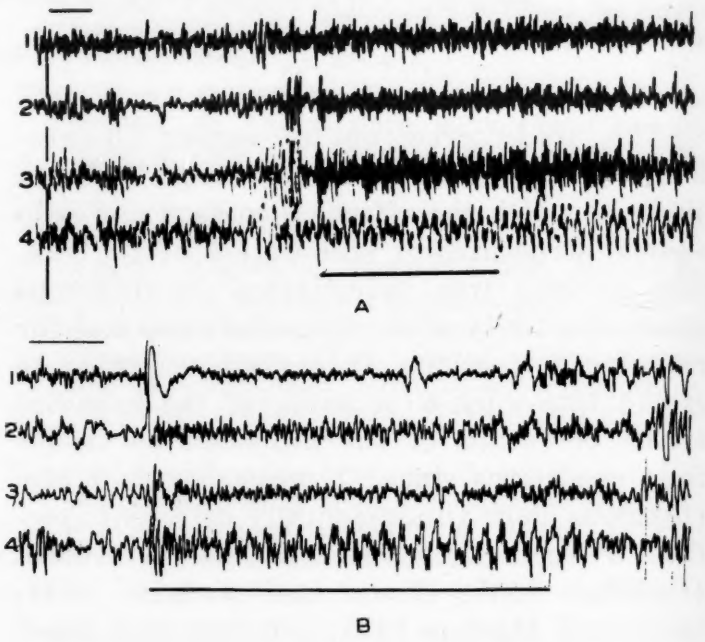


Fig. 2
A. Effect on neocortex and hippocampus of stimulation of the central end of the l. splanchnic nerve. 1. l. ant. sigmoid gyrus; 2. l. lateral gyrus; 3. l. middle suprasylvian gyrus; 4. l. hippocampus. Horizontal bar indicates stimulation (16 V. 0.5 msec. 120/sec. for 5 sec.).
B. Effect of stimulation of the central end of l. vagus on neocortex and hippocampus. 1 to 4 as in A. Stimulus: 9 V., 0.5 msec., 120/sec. for 5.5 sec. Note the faster speed of recording in B.

Since CO_2 has been shown to produce a powerful arousal reaction (Gellhorn 1953 a and b) its influence on the electrogram was investigated. Thirty-five per cent CO_2 was used, which during the first minute caused a marked excitation of the ECG and the hypothalamus, whereas these areas are depressed in later phases of CO_2 inhalation. Figure 3 shows an increase in frequency and amplitude in the ECG recorded from the suprasylvian gyrus, whereas the slow potentials of the hip-

TABLE I

The effect of stimuli of varying intensities on the frequency of the synchronous discharges of the hippocampus*

Voltage	Hyppocampal Potentials Frequency/sec.
I. Stimulation of the central end of the ipsilateral vagus.	
5	4
6	4
7	4.3
9	4.5
II. Stimulation of the central end of the ipsilateral splanchnic.	
13	3.0
16	3.3
20	4.5
III. Stimulation of the ipsilateral caudate nucleus	
20	2.5
22	3.0
24	3.5
27	4.5

* Frequency of stimulation: 120/sec.

pocampus became gradually regularized and increased in amplitude and frequency. Here it is noted again, as in the experiments on stimulation of afferent nerves, that the changes induced by CO_2 occurred earlier in the neocortex than in the hippocampus.

The frequency analysis (Offner analyser) showed that the maximum of the integrated amplitude shifted from 2.5/sec. in A to 4/sec. in B.

Although the changes in the electrogram were similar to those produced by stimulation of afferent nerves, quantitative differences existed. The action of CO_2 was more effective and produced characteristic changes even in those cats in which nerve stimulation failed to alter the electrogram of the hippocampus.

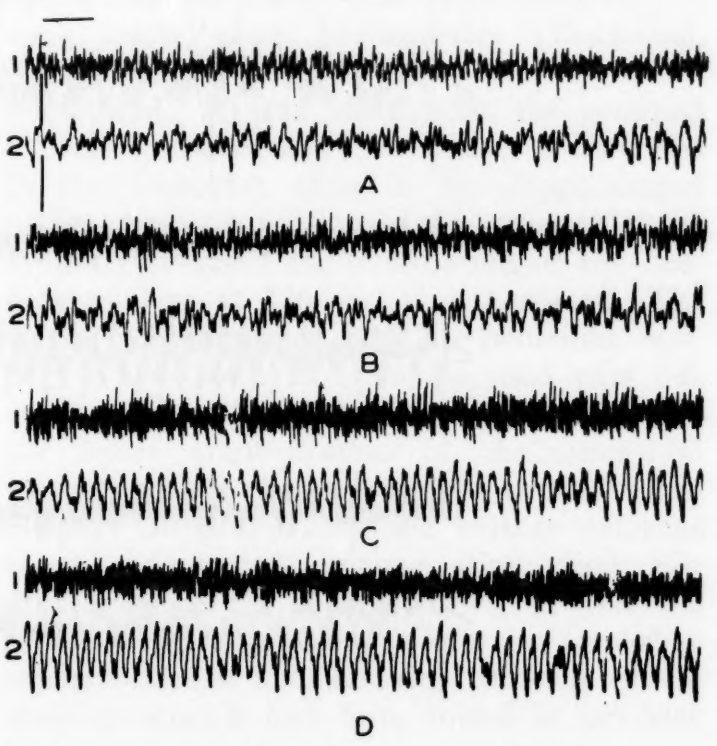


Fig. 3

Effect of CO_2 inhalation (35 per cent) on neocortex and hippocampus. 1: l. middle supersylvian gyrus; 2. l. hippocampus. A, before CO_2 inhalation; B, 10 sec. after the onset of CO_2 inhalation; C, 5 sec. after B; D, 18 sec. after C.

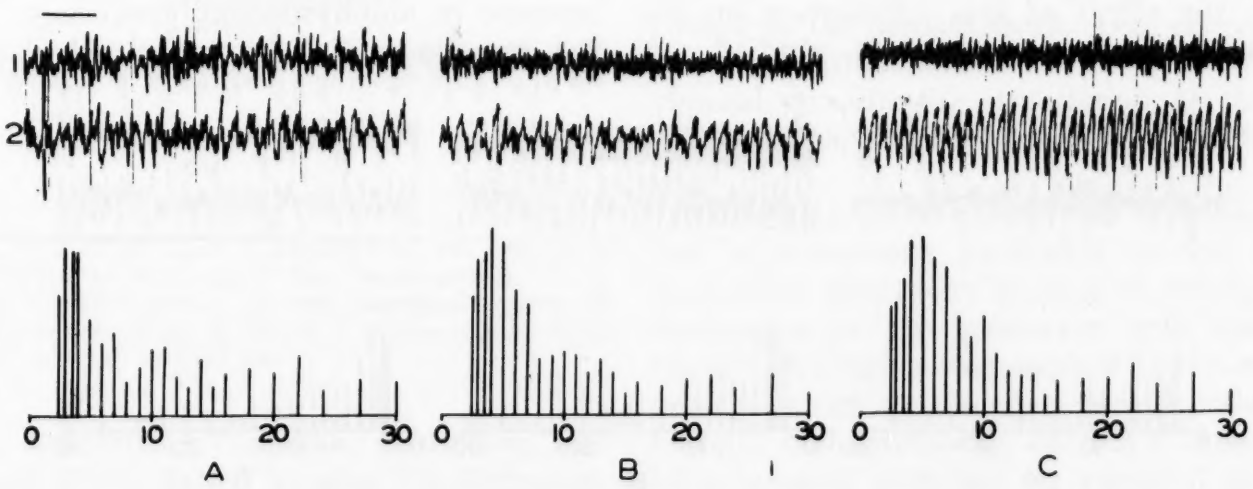


Fig. 4

Effect of CO_2 inhalation (35 per cent) on neocortex (1) and hippocampus (2). The histograms indicate the frequency analysis (abscissa: cycles per sec.) of the hippocampus. A, before; B, 15 sec. after the onset of CO_2 inhalation; C. 25 seconds after B.

2. *The Influence of Stimulation of the Caudate Nucleus on the EEG of the hippocampus.*

Since stimulation of the caudate nucleus at 120/sec. elicits an alerting reaction in the typical effect is illustrated in figure 5. It is seen that activation of the caudate nucleus alters neocortex and hippocampus in the same manner as increased afferent impulses. Part B of figure 5 shows clearly that the sinusoidal

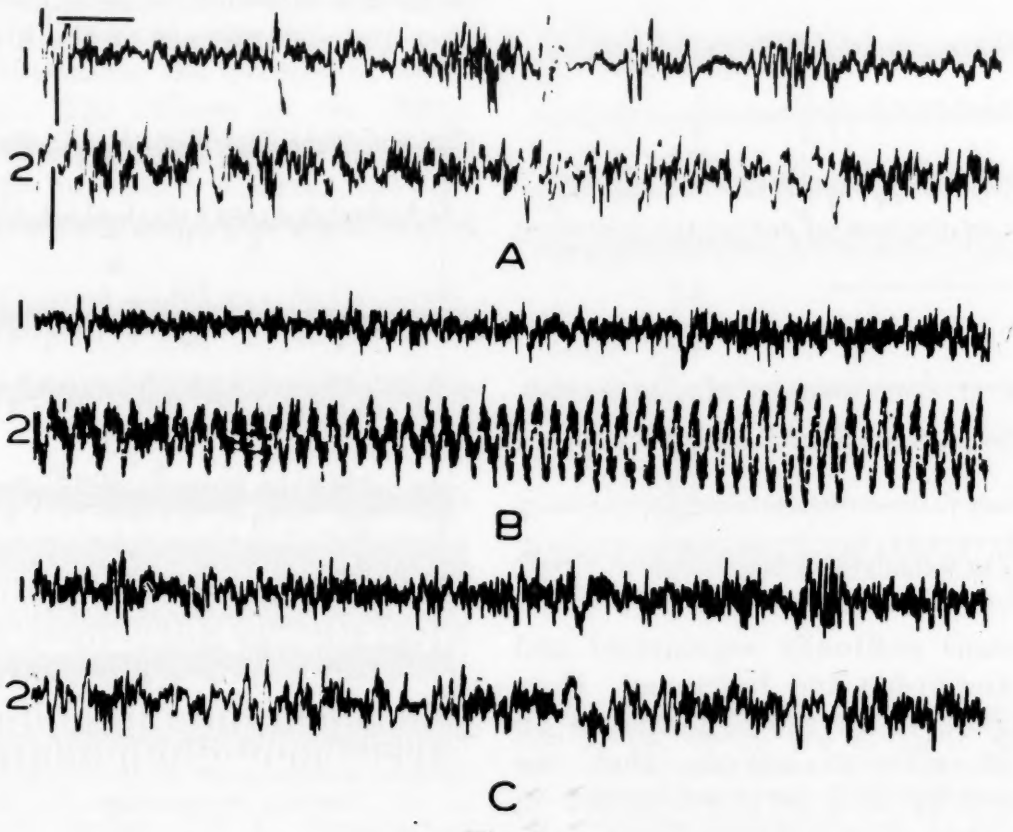


Fig. 5

Effect of stimulation of the caudate nucleus on neocortex and hippocampus. 1. l. middle suprasylvian gyrus; 2. l. hippocampus. A, before; B, during; C, 16 sec. after stimulation (20 V. 0.5 msec., 120/sec.).

ECG of the neocortex (Stoupel and Terzuolo 1954; Tokizane, Kawakami and Gellhorn 1957), the effect of this stimulation on the hippocampal electrogram was studied. A waves in the hippocampus become increasingly regular during the period of stimulation and increase in amplitude and frequency. As in the experiments involving the stimulation of

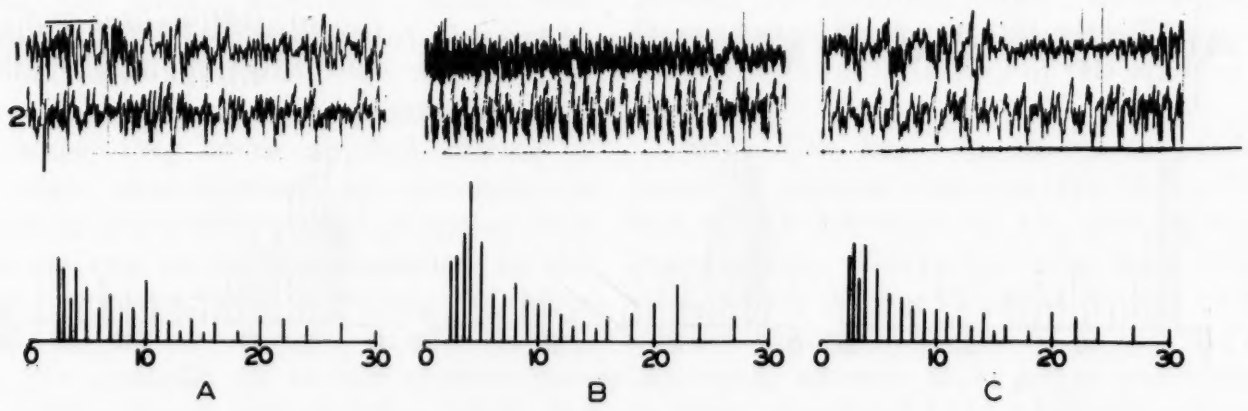


Fig. 6

Effect of stimulation of the caudate nucleus (8.5 V., 0.5 msec. 120/sec.) on the 1. l. middle suprasylvian gyrus; 2. hippocampus. The histograms indicate the frequency analysis of the hippocampus. Two 10″ periods were averaged. A, before; B, during; C, 20 sec. after stimulation.

cutaneous sense organs or afferent nerves it was found that the increase in amplitude and also the increase in frequency of the hippocampal waves were enhanced with either increasing intensity or duration of stimulation of the caudate nucleus. The frequency analysis of the hippocampal potentials under these conditions disclosed a marked increase in the integrated amplitude of the potentials of low frequencies with a shift in the maximum from 2.5 sec. to 4/sec. (fig. 6). There was also a slight change in faster potentials with a shift in the maximum from 20 to 22/sec., but this phenomenon was not constant.

Table I shows a typical experiment in which the influence of the stimulation of visceral nerves and of the caudate nucleus on the hippocampal potentials is illustrated. It is shown that with increasing intensity of stimulation of the vagus or splanchnic nerves or of the caudate nucleus, the frequency of the hippocampal potentials increases.

A second group of experiments was performed with stimulation of the caudate nucleus with a single shock (square wave). This stimulus, which elicits characteristic spindles

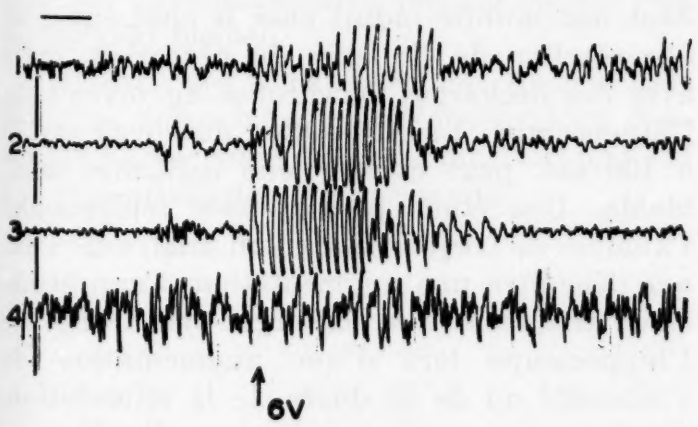


Fig. 7

Effect of a single shock (indicated by the arrow) to the caudate nucleus upon the hippocampus. 1. l. anterior sigmoid gyrus; 2. left marginal gyrus; 3. l. middle suprasylvian gyrus; 4. l. hippocampus. Calibration: 100 μV. and 0.5 sec.

in the neocortex (Tokizane, Kawakami and Gellhorn 1957), failed to alter the hippocampus at threshold and suprathreshold intensities (fig. 7). In some experiments in which this stimulus was applied repeatedly at intervals of 0.2, 0.5 or 1.0/sec., some slight shift in the electrogram of the hippocampus occurred, suggesting an increasing dominance of the "fast" potentials.

3. *The Influence of Anesthesia on the Hippocampus.*

Although the main experiments were performed on curarized cats, some observations were made after barbiturates (Pentothal, Nembutal, or Dial-Urethane) had been administered. It was noted that the grouped ("Dial") potentials were more prominent in the neocortex than in the hippocampus under these conditions. As expected, the arousal threshold for stimulation of the caudate nucleus at 120/sec. was increased. The effect of stimulation was, in principle, similar to that seen in unanesthetized cats but weaker, as indicated by its shorter duration, the lesser augmentation of the sinusoidal waves and the lesser increase in their frequency. In deep anesthesia neither afferent nerve nor caudate nucleus stimulation, nor inhalation of 35 per cent CO_2 altered the hippocampal potentials, in contrast to earlier reports (Green and Arduini 1954) in which alerting stimuli had been found to produce fast activity in the hippocampal record.

DISCUSSION

That alerting stimuli produce synchronous discharges in the hippocampus while asynchrony prevails in the neocortex (Green and Arduini 1954; Rimbaud *et al.* 1955)) was confirmed in the present work. Our experiments show that this statement is valid also for visceral stimuli, the stimulation of the caudate nucleus at 120/sec. and the action of CO_2.

The attempt to show the dominance of fast asynchronous potentials in the hippocampus in conditions leading to synchronous discharges in the neocortex was less successful. A single shock applied to the caudate nucleus which produced a burst of slow potentials in the neocortex did not influence the hippocampus, although on repeated application of such stimuli a tendency toward asynchrony appeared in some hippocampal records. It should be mentioned that Rimbaud, Passouant and Cadilhac (1955) observed in cats

with chronically implanted electrodes a period of desynchronization of the hippocampus when they fell asleep. This desynchronization preceded the synchronization of the neocortex. In deep sleep, however, slow potentials appeared in neocortex and hippocampus.

Our chief finding is the fact that under the influence of afferent stimuli, inhalation of CO_2, and stimulation of the caudate nucleus at 120/sec. the synchronous slow activity in the hippocampus increases in amplitude and frequency.[1] These changes, confirmed by frequency analysis, seem to indicate that the two phenomena, shift in the maximal electrical output to a higher frequency and increase in the amplitude of the potentials which characterize cortical excitation, are present in the hippocampal records. There is, however, a fundamental difference between the excitatory processes of the neocortex and those of the hippocampus under these conditions. Frequency analysis shows that cortical excitation resulting from nociceptive stimulation, inhalation of CO_2 (Gellhorn, unpublished experiments) and baroreceptor reflexes (Nakao, Ballin and Gellhorn 1956) is characterized by a diminution in the height of the integrated waves of low frequency and by an increase in those of high frequency with the maximum occurring at ranges of 15 to 18 or even 20-30/sec. On the other hand, the changes in hippocampal potentials described in this paper were shown to be restricted to a narrow band of low frequencies (2.5 to 5.0/sec.). The reason for this peculiar reactivity of the hippocampus is not known, and attempts to correlate the occurrence of slow waves with unit potentials under conditions of arousal (Green and Machne 1955) have thus far largely failed.

SUMMARY

Stimulation of sense organs and afferent nerves (also from the viscera) and inhalation of 35 per cent CO_2 for 1 min. induce an alerting reaction in the neocortex but synchronous discharges in the hippocampus of curarized cats. Stimulation of the caudate nucleus at 120/sec. exerts a similar action. Closer study including frequency analysis with an Offner analyser shows that the synchronous discharges in the hippocampus increase in amplitude and frequency with increasing intensity or duration of stimulation. This suggests that the characteristics of cortical excitation, shift of the maximum in the frequency spectrum to a higher frequency and increase in the amplitude of the potentials, are present in the hippocampus in the above mentioned experimental conditions, although they are confined to the frequencies of 2.5 to 5.0/sec.

Stimulation of the caudate nucleus with single shocks which produce a burst of slow waves in the neocortex do not alter the hippocampus.

The effect of alerting stimuli on neocortex and hippocampus is diminished or abolished in anesthesia.

RÉSUMÉ

La stimulation des organes de sens et des nerfs afférents (y compris ceux des viscères) et l'inhalation de CO_2 30-35 pour cent pendant une minute induit chez le chat curarisé une réaction de vigilance du néocortex, mais avec des décharges synchrones au niveau de l'hippocampe. La stimulation du noyau caudé à 100/sec. peut exercer une influence semblable. Une étude plus poussée comprenant l'analyse de fréquence avec un analyseur Offner démontre une augmentation d'amplitude et de fréquence des décharges synchrones de l'hippocampe lors d'une augmentation de l'intensité ou de la durée de la stimulation. Ceci suggère que les caractères du déplacement de l'excitation corticale maximum dans le spectre de la fréquence à une fréquence et un recrutement plus élevés, sont présents dans l'hippocampe dans les conditions d'expérimentation ci-haut mentionnées, quoiqu'ils se trouvent limités à des fréquences de 2.5 à 5.0/sec.

La stimulation du noyau caudé par des chocs uniques qui déclenchent une bouffée d'ondes lentes dans le néocortex ne modifie pas l'hippocampe.

[1] Gangloff and Monnier (1956) claim that arousal causes an acceleration in the slow rhythmic activity of the rhinencephalon but the illustrations of the authors are unconvincing.

L'effet des stimuli vigilants sur le néocortex et sur l'hippocampe se trouve être diminué ou aboli sous l'effet de l'anesthésie.

ZUSAMMENFASSUNG

Reizung kutaner Sinnesorgane und sensorischer Nerven (einschl. des Vagus und N. splanchnicus) und Inhalation von 35 Prozent CO_2 für eine Minute ruft eine Weckreation im Neokortex, aber synchrone Entladungen im Hippocampus kurarisierter Katzen hervor. Reizung des N. caudatus mit elektrischen Strömen von 120/Sek. übt eine ähnliche Wirkung aus. Frequenzanalyse mit dem Offner'schen Analysator zeigt, dass die synchronen Entladungen im Hippocampus in Amplitude und Frequenz zunehmen, wenn die Intensität oder Dauer der Reizung wächst. Diese Beobachtungen lassen erkennen, dass die charakteristischen Anzeichen kortikaler Erregungen, die Verlagerung des Maximum der integrierten Potentiale auf eine höhere Frequenz und die Zunahme der Amplitude der Potentiale, an dem Elektrogram des Hippocampus unter den beschriebenen Bedingungen auftreten, obwohl diese Veränderungen auf den Frequenzbereich von 2.5 bis 5.0/Sek. beschränkt bleiben.

Reizung des N. caudatus mit Einzelreizen, die eine Salve langsamer Potentiale im Neokortex hervorrufen, haben keine Wirkung auf die Potentiale des Hippocampus.

Der Weckeffekt verschiedener Reize auf Neokortex und Hippocampus ist in Narkose vermindert oder beseitigt.

REFERENCES

CADILHAC, J. *Hippocampe et Epilepsie.* Montpellier, **1955.**

GANGLOFF, H. and MONNIER, M. Electrographic aspects of an "arousal" or attention reaction induced in the unanesthetized rabbit by the presence of a human being. *EEG Clin. Neurophysiol.*, **1956**, *8*: 623-629.

GELLHORN, E. The physiological basis of the carbon dioxide therapy of psychoneuroses. *J. Ment. Sci.*, **1953**a, *99*: 357-373.

GELLHORN, E. On the physiological action of CO_2 on cortex and hypothalamus. *EEG Clin. Neurophysiol.*, **1953**b, *5*: 401-413.

GELLHORN, E. Unpublished experiments.

GREEN, J. D. and ARDUINI, A. A. Hippocampal electrical activity in arousal. *J. Neurophysiol.*, **1954**, *17*: 533-557.

GREEN, J. D. and MACHNE, X. Unit activity of rabbit hippocampus. *Amer. J. Physiol.*, **1955**, *181*: 219-224.

LIBERSON, W. T. and AKERT, K. Hippocampal seizure states in guinea pig. *EEG Clin. Neurophysiol.*, **1955**, *7*: 211-222.

NAKAO, H., BALLIN, H. M. and GELLHORN, E. The role of the sino-aortic receptors in the action of adrenaline, noradrenaline and acetylcholine on the cerebral cortex. *EEG Clin. Neurophysiol.*, **1956**, *8*: 413-420.

RIMBAUD, L., PASSOUANT, P. et CADILHAC, J. Participation de l'hippocampe à la régulation des états de veille et de sommeil. *Rev. Neurolog.*, **1955**, *93*: 303-308.

STOUPEL, N. et TERZUOLO, C. Etude des connexions et de la physiologie du noyau caudé. *Acta Neurol. Psychiat. Belgica*, **1954**, *54*: 239-248.

TOKIZANE, T., KAWAKAMI, M. and GELLHORN, E. On the relation between the activating system and the recruiting system. *Arch. intern. physiol.*, **1957**, *95*: 415-432.

Reference: TOKIZANE, T., KAWAKAMI, M. and GELLHORN, E. Hippocampal and neocortical activity in different experimental conditions. *EEG Clin. Neurophysiol.*, **1959**, *11*: 431-437.

PRINTED IN CANADA

IMPORTANT ANNOUNCEMENT

TO AUTHORS

TO CONDENSE PAPERS AND ABSTRACTS SUBMITTED

TO THE EEG JOURNAL

We regret that it has become necessary to abandon our lenient policy with regard to length of manuscripts and abstracts to be published in our Journal. We share, with other journals specializing in the neurological sciences, the healthy dilemma of too many manuscripts and Society Proceedings. The large backlog forces us into unwanted delays in publication. We have tried to meet this challenge by publishing supplements and increasing numbers of pages in each issue but excessive printing costs makes it necessary to restrict this policy.

Regular Manuscripts

Maximum length for regular manuscripts should not exceed four thousand (4,000) words. This is about 20 pages of double space typed copy, or 30 pages of triple spaced copy on standard 8½ x 11 inch. paper. This should include references. Review of literature and discussion should be especially reduced to the minimum. In most cases six carefully chosen and prepared illustrations should be adequate. Short summaries of not more than 200 words should be provided for translation into other languages.

Technical or Clinical and Laboratory Notes

These notes should not exceed one thousand (1,000) words and usually less than this is sufficient, with one or two illustrations.

Abstracts for Society Proceedings

Each abstract should not exceed 200 words with no illustrations.

CEREBELLO-HIPPOCAMPAL INFLUENCES ON THE ELECTROENCEPHALOGRAM [1]

KINJIRO IWATA, M.D.[2] and RAY S. SNIDER, Ph.D.
Department of Neurology and Psychiatry and Department of Anatomy, Northwestern University, Chicago, Ill.

(Received for publication: September 7, 1958)

Starting with the discovery of tactile, auditory and visual areas in the cerebellum (1944), recent neurophysiological studies indicate that cerebellar function is much broader than has hitherto been accepted. Whiteside and Snider (1953) demonstrated electrically that there are extensive connections of this organ to the upper brain stem and reticular formation. Cooke and Snider (1953) were able to elicit activation of the cerebral cortex by cerebellar stimulation. Very recently Schoolman and Delgado (1958) reported that the neocerebelum maintains a role in the facilitation and inhibition of cerebrally induced movement. With so broad an ascending influence, it occurred to the present investigators that the cerebellum may also have a functional relationship with an older part of the brain, *i.e.*, the rhinencephalon. This appeared to be even more probable in view of Morin and Green's (1953) demonstration that seizure activity can exist within the cerebellum as a result of hippocampal stimulation. Kaada's (1951) extensive study on the rhinencephalon was used as a basis for hippocampal influences on the cerebrum. Accordingly, in the present experiments, standard electrophysiological recording and stimulation techniques have been used to study cerebello-hippocampal relationships.

MATERIALS AND METHODS

The data presented here were collected from 24 healthy adult cats (Felis domestica), weighing between 2.5 and 3.5 kg. The animals were anesthetized with ether, and the surgical procedures of exposing the brain were promptly carried out. A tracheotomy was done, after which 20-30 mg. of Flaxedil (American Cyanamid Company) was administered and the animal attached to a respirator, to which a small amount of O_2 was added continuously. Two per cent procaine was infiltrated around all incisions. The exposed nervous tissues were bathed with warm saline and mineral oil. Care was also taken to keep the systemic temperature of the animal from falling.

Bipolar silver wire electrodes were used for pial recording and stimulation; stereotaxically oriented bipolar nichrome wire electrodes, insulated except for the tips, were used for recording from deeper structures. Histological studies were made, using the Klüver and Barrera stain on all areas in which either depth recording or stimulation was used.

All records included in the present report were taken on a Grass 8-channel electroencephalograph, although for cerebellar recording it was often necessary to monitor the activity with a cathode ray oscilloscope. Electrical pulses were given by means of a Grass S4A stimulator. The usual voltage range for stimulation was 5 to 15 V., although (as indicated below) it was necessary to use higher voltages in many cases. Unless otherwise noted, 1 msec. biphasic pulses were used. The usual electrode to tissue resistance was 5,000 to 12,000 ohms. The higher values were usually observed near the end of the experiment, or if clotted blood interfered with proper contact. Chloriding the tip of the silver wire electrode was routinely done at the beginning of an experiment. The usual current flow from a single pulse was one milliampere.

[1] This research work was financed by the U. S. Public Health Service Grant-in-Aid Program.

[2] Present address: University of Nagoya, School of Medicine, Nagoya, Japan.

RESULTS

The so-called "resting" cerebral activity of the cat shows a frequency of 8-15 waves per sec., and an amplitude of 100-300 μV. It can be changed readily to an arousal or activated cortical pattern by electrical stimulation of the cerebellum at parameters of 5-25 V. and frequencies of 10 to 200 pulses per sec. Throughout these studies, as shown in figure 1, stimulation of the tuber vermis at 5 V. 100/sec. changes the irregular patterns of the left and right cerebral cortices (in this case, the suprasylvian gyri) to low voltage fast frequencies. However, note that at the same time hippocampal activity is changed to moderate voltage slow waves. As shown in the second row of traces, a similar result is obtained with 10 V. stimulation. In the third row of traces a slower frequency of cerebellar stimulation, *i.e.*, 30/sec., produces a like

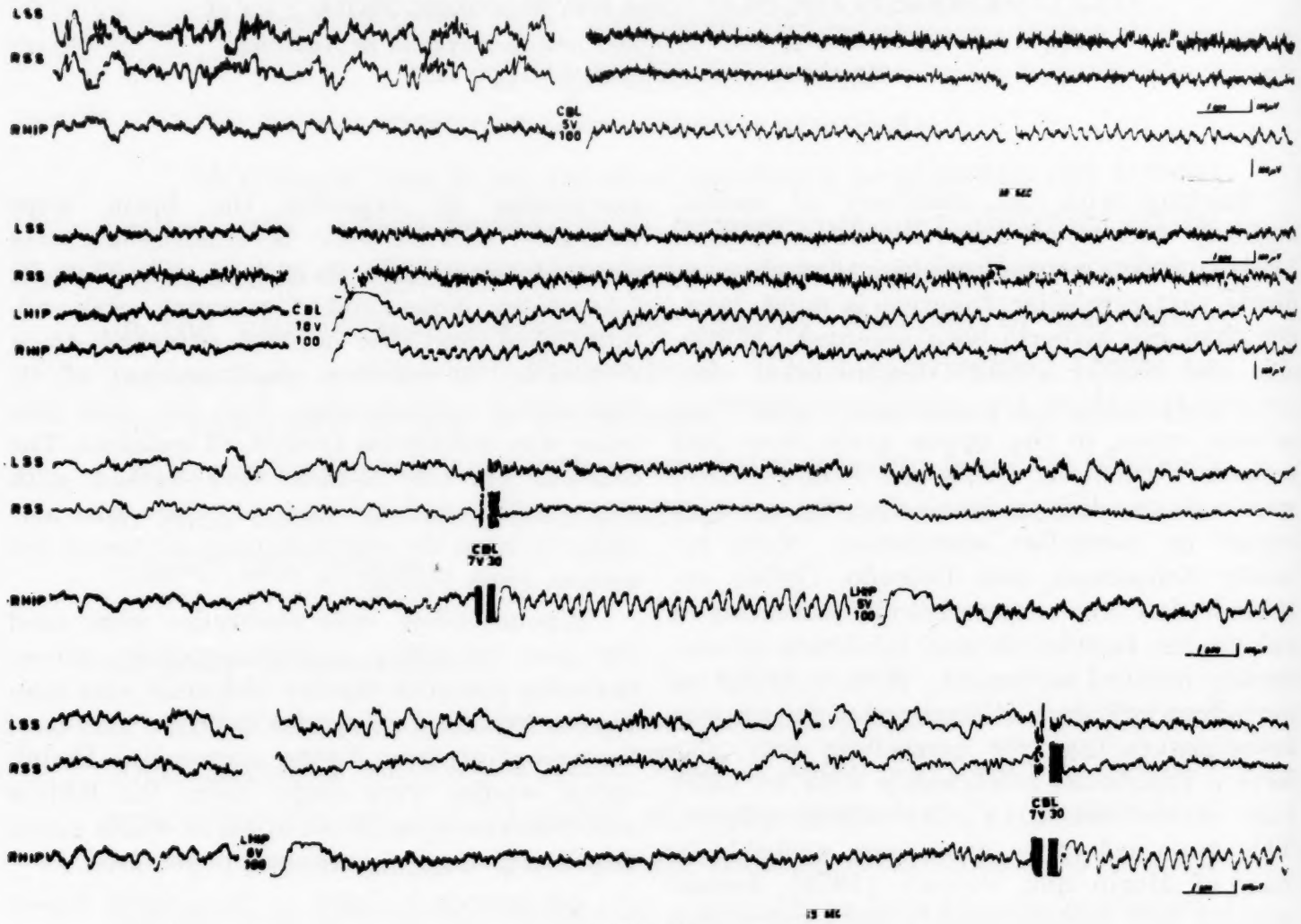
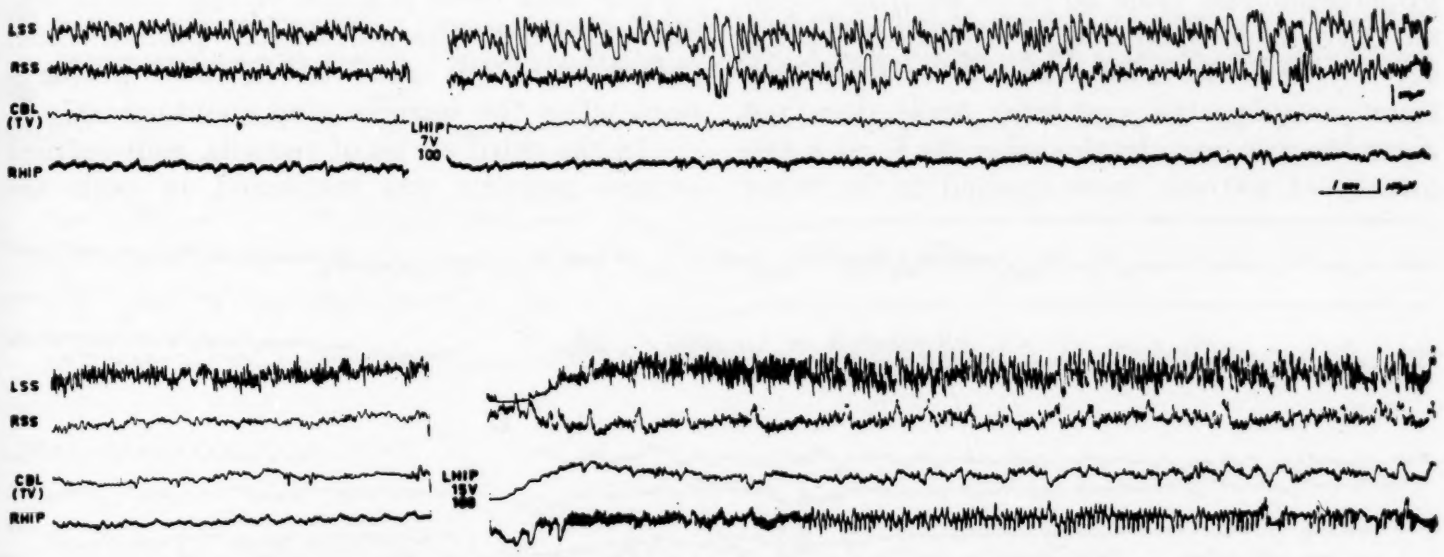


Fig. 1

Electrical recording from the left and right suprasylvian gyri (LSS, RSS) and left and right hippocampi (LHIP, RHIP) following electrical stimulation of the hippocampus and cerebellum. Square wave pulses of 1 msec. duration, ranging between 5 and 10 V., were used. Frequency of stimulation was either 30 or 100/sec. Average electrode resistance was 10,000 ohms.
In the upper traces, 5-V. pulses at a frequency of 100/sec. were applied to the pial surface of the tuber vermis. Note that 10 sec. have been removed from the post-stimulatory portion of the record. The second series resemble the first, except that 10-V. stimulation was used, and the record is continuous. In the third group, 7-V. pulses at a frequency of 30/sec. were applied to the tuber vermis, and 7 sec. later the left hippocampus was stimulated with 5-V. at 100/sec. In the bottom series of traces, the hippocampus (left) was stimulated first, and 27 sec. later the cerebellum was stimulated. 100-μV. time signals are given, and 1-sec. time markers are included. All records were taken on a standard EEG machine by way of silver-silver chloride pial electrodes and nichrome wire depth electrodes. Cats were used, anesthetized by ether and Flaxedil.

change. When followed by hippocampal stimulation (5 V. at a frequency of 100/sec.), fast activity appears in the hippocampus, with slowing in the ipsilateral cerebral cortex. If higher voltage pulses are given to the hippocampus, the cerebral slow waves appear bilaterally. In the fourth row of traces, note that there are simultaneous slow waves in the hippocampus and low voltage fast waves in the cortex. Hippocampal stimulation (6 V. at 100/sec.) introduces fast activity in the hippocampus, accompanied by high voltage slow waves in the cerebral hemispheres (in this case, the suprasylvian gyri). This pattern can be reversed by cerebellar stimulation, as shown in the last part of the record, at which point a frequency of 30/sec. (7 V.) was applied to the tuber vermis.

Figure 2 shows the results obtained when higher voltage pulses were given to the hippocampus. As illustrated in the upper row of traces, 7 V. can induce high voltage slow and fast waves in the cerebrum more prominent ipsilaterally, whereas low voltage fast activity continues in the hippocampus. In more susceptible animals it was possible to induce seizure activity in both the cerebral cortex and hippocampus at this voltage. These types of seizure discharges are shown in the second row of traces, in which 15 V. at a frequency of 100/sec. were applied to the left hippocampus. Note that initially the seizure activity involves the ipsilateral suprasylvian cortex as well as the contralateral hippocampus. Although not illustrated here, the ipsilateral hippocampus is also involved. It



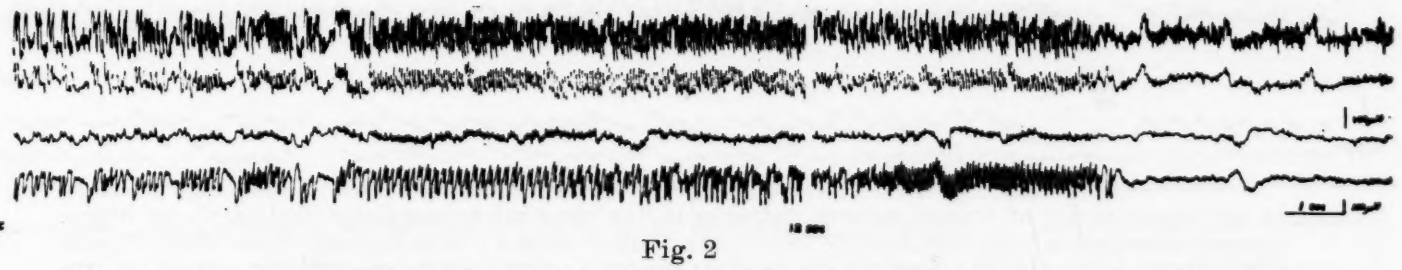


Fig. 2

This chart shows the results of applying higher voltage (7 and 15) square wave pulses of 1 msec. duration to the hippocampus. Current flow ranged between 1 and 1.6 mA. In the upper series of traces, note the high voltage mixed slow and fast waves in the left and right suprasylvian gyri (LSS: RSS) resulting from stimulation of the left hippocampus (LHIP) with 7 V. at a frequency of 100/sec. In the second group, 15 V. applied to the left hippocampus induced seizure activity in the contralateral hippocampus and ipsilateral cerebral hemisphere (left suprasylvian gyrus), which spread to the right suprasylvian gyrus and cerebellum. The third series are a continuation of the second. Experimental conditions resemble those described for figure 1.

has a lower seizure threshold than the contralateral. However, the seizure activity rapidly spreads to the contralateral cortex and cerebellum, as shown in the bottom set of traces.

Figure 3 indicates that cerebellar stimulation can alter seizure patterns in the cerebrum initiated by hippocampal stimulation (see top set of traces). Since such seizures in a routine preparation last from 30 to 90 sec., this could not have been spontaneous alteration of the activity. Furthermore, when the seizures stop spontaneously, the post-ictal trace does not resemble this one. In this case, 20 V. at a frequency of 100/sec. were applied to the tuber vermis. Note that not only did the seizure patterns stop, but they were replaced by an activation pattern in the left and right suprasylvian gyri, and by slowing in the hippocampus. The bottom series of traces are a continuation of the top, with a 5-sec. omission. In this case 20 V. applied to the left hippocampus reinstated mild seizure discharges in the two cerebral cortices.

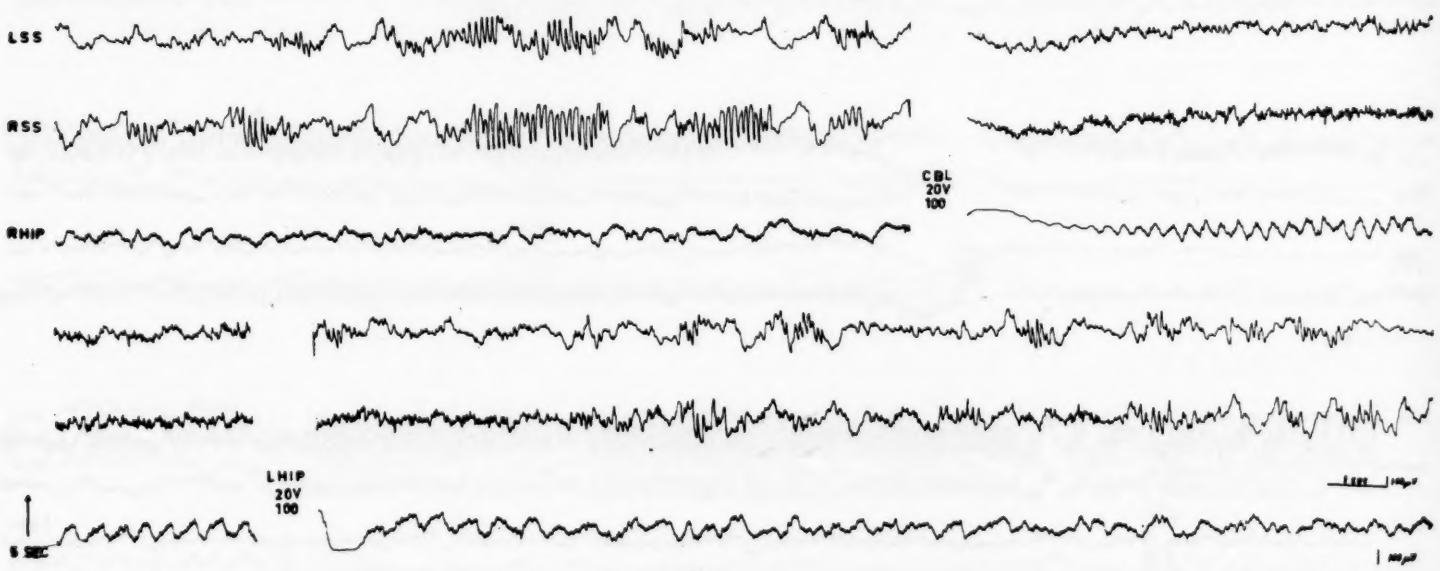


Fig. 3

In the upper series of traces, seizure patterns in the cerebral hemispheres (initiated by hippocampal stimulation) are blocked by cerebellar (tuber vermis) stimulation. Note that a poststimulatory activation pattern exists in the cerebrum, and synchronized slow waves in the hippocampus. The lower series of traces is a continuation of the upper, with a 5-sec. interval removed. Note that restimulation of the hippocampus (20 V. at a frequency of 100/sec.) reintroduces the seizure-like patterns in the cerebrum. Experimental conditions are similar to those described for figures 1 and 2.

Figure 4 shows data collected when stimulation to the hippocampus is severe enough to induce seizure activity, and shows the effect of additional cerebellar activation upon it. As indicated in the upper series of traces, only 7 V. (100/sec.) applied to the hippocampus (in this instance the right side) are necessary to produce long, sustained activity in the cerebrum. Cerebellar stimulation can "break up" these seizure patterns (illustrated in the second series of traces). This group is a continuous run from the above-mentioned. Note further that there is a low voltage activation-like pattern in the post-seizure period. Such patterns are not observed in these preparations when the seizures stop spontaneously.

In the third series of records, well-defined seizure activity was instituted in both the left (not shown) and right hippocampi by 15-V. stimulation. It was promptly disrupted by applying 7-V. electrical pulses to the cerebellum. As in the above data, a poststimulatory activation trace results. In the bottom series are illustrated an unusual condition in which it was possible to set up seizure activity in the nucleus centrum medianum by stimulation of the hippocampus with as little as 3 V. As indicated in the continuous record, cerebellar activation (10 V., 30/sec.) was effective in disrupting the activity.

If an electrical stimulus delivered to the hippocampus is strong (usually 15 V. or over), immediate cortical seizure patterns appear bilaterally, generally starting with high voltage spikes and terminating with mixed spikes and slow waves. However, if there is considerable mechanical manipulation of the hippocampus, spontaneous paroxysmal activity may occur; or, in very sensitive animals, seizures can be induced with as few as 3 V. The usual effect of low voltage stimulation (3-7 V.) is slowing of cortical frequencies. Morin and Green (1953) saw similar slowing in the guinea pig. Frequency of stimulation did not appear to be critical, since any value between 5 and 200 could be used. It should be pointed out that cortical slowing by hippocampal stimulation is not always easy to elicit, because if stimulation is weak, slow wave patterns are difficult to recognize against a variable EEG background; an increase of voltage often induces seizures which disturb the record. Often it is the animal in a so-called "alerted" state that responds best. Under such conditions, the 3-6/sec. slowing is easily recognizable. It appears ipsilaterally and gradually spreads to the contralateral hemisphere.

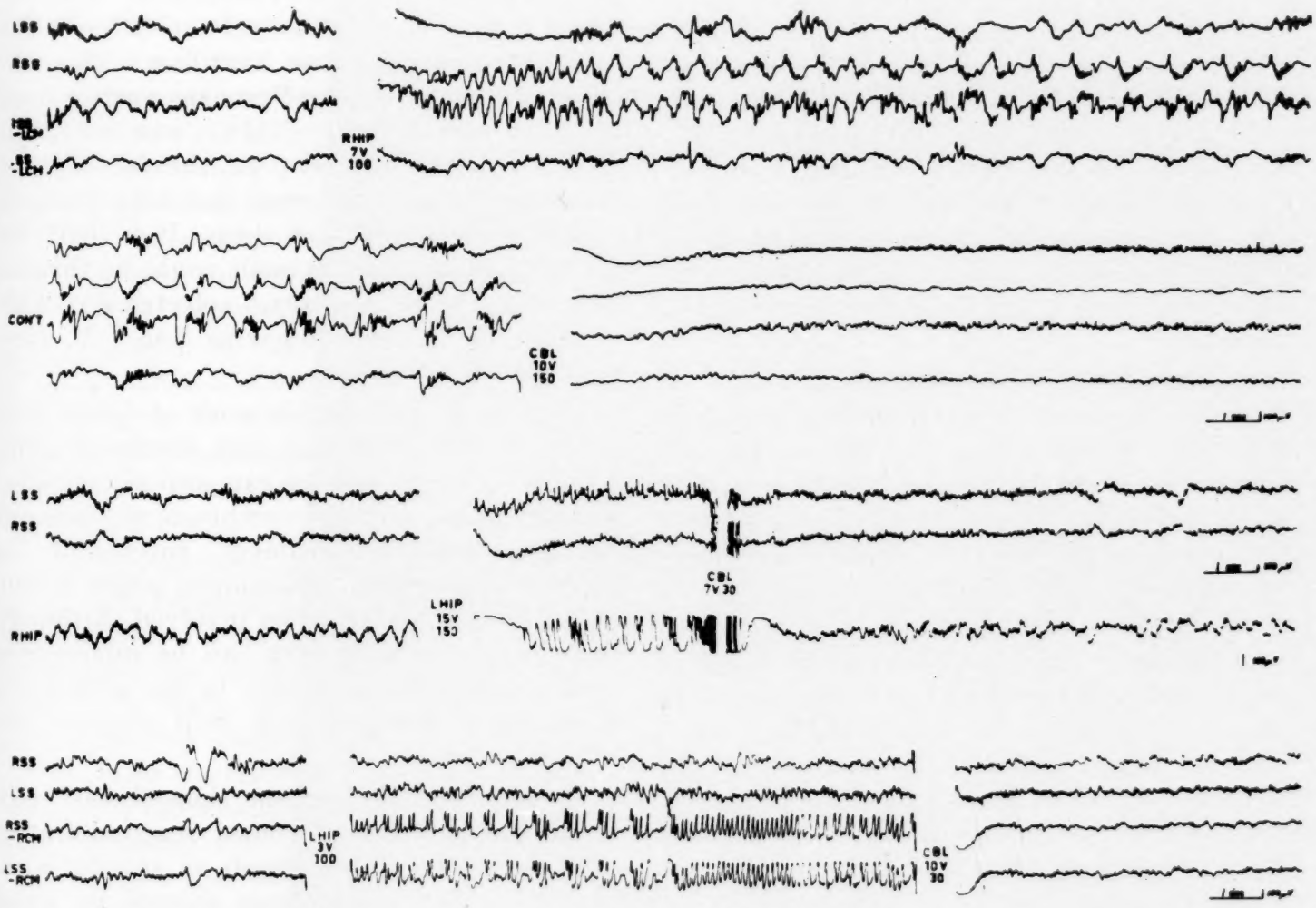


Fig. 4

This shows a series of traces in which seizures were inhibited by cerebellar (tuber vermis) stimulation. The second group is a continuation of the first. Note in the third series that the seizure is largely limited to the hippocampus. In the bottom traces, activity in both cerebral hemispheres and the right nucleus centrum medianum of the thalamus was sampled. It is unusual to find seizure induction with as little as 3 V. applied to the hippocampus, although mechanical manipulation can often do so. Note how promptly cerebellar stimulation stops the seizure. All experimental conditions resemble those described in figure 1. Cats were under ether and Flaxedil anesthesia; 100-μV. and 1-sec. calibration signals were used.

DISCUSSION

The present work clearly demonstrates that cerebellar stimulation can produce an activation-like response in the cerebral hemispheres. This finding was expected in view of Hassler's (1951) work on the human, and Rand's (1954) work on the monkey, showing that the brachium conjunctivum has extensive connections, not only to the mesencephalic tegmentum, but also to the nucleus centrum medianum, as well as to the intralaminar thalamic nuclei. Whiteside and Snider (1953) have electrophysiologically demonstrated connections to these areas from the cerebellum of the cat; previously, Ranson and Ingram (1932), by means of a fiber degeneration technique, had noted similar connections to the thalamus.

In view of the above studies and those of Rose and Woolsey (1949), showing by means of retrograde cell change that the midline and intralaminar nuclei project to the so-called rhinencephalon, the possibility of a cerebellar influence being exerted upon the rhinencephalon by way of these thalamic nuclei might be considered.

Studies by the present authors confirm the extensive observations of Green and Shimamoto (1953) on the seizure characteristics of the hippocampus. By regulating the strength of the stimulus, the induced seizure activity can be limited to the hippocampus (ipsilateral first, then spreading to the contralateral side). If higher voltage pulses are used, seizure activity becomes generalized, involving both cerebral hemispheres and the cerebellum. These discharges show a very regular pattern and frequency in the 22-25/sec. range; usually they terminate abruptly without a well-defined isoelectric period (see Liberson and Akert 1955). Such patterns are easy to elicit. It was common to see short bursts of them as a result of the mechanical irritation of inserting the recording electrode. When the hippocampus was exposed surgically, slight manipulation of the structure with forceps was adequate to initiate seizure activity in many instances. Fortunately, this activity was short-lived and could always be blocked by Nembutal anesthesia. However, this last procedure was rarely used, because the threshold of response after barbiturate administration was raised so high that it was difficult to work with the animal. This applied to both the hippocampal and cerebellar systems.

Slowing of cortical frequencies was observed following hippocampal activation if the stimulating voltage was kept low. This observation on the cat confirms the earlier ones of Green and Arduini (1954), who noted an inverse relationship between the patterns of discharge in the neocortex and hippocampus in both wakefulness and sleep. It is difficult to explain why some animals could be thrown into seizure-like patterns (electrical) with stimulating voltages as low as 3 to 7 V. (approximately 0.5 mA.).

In view of the earlier work of Cooke and Snider (1955), showing that electrical stimulation of the cerebellum can stop electrically-induced seizures of the cerebrum, the present authors were particularly interested in whether or not the hippocampus might be one of the intermediate centers involved. Although some of the present data can be interpreted in this manner, the answer to the problem is much more complex and will require additional work.

When the corticogram showed fast patterns, due not to an arousal reaction but to local irritative causes (such as subpial hemorrhage), the hippocampus showed its usual resting patterns independent of the activity in the cortex. Cerebellar stimulation was able to induce characteristic synchronized slow wave patterns in the hippocampus, despite any obvious activation effects on the corticogram as a result of the irritation. This indicates that cerebellar influences need not modify cortical activity before introducing slow waves in the hippocampus. This reinforces the authors' belief that the cerebellum acts on the hippocampus by way of a subcortical center, perhaps the thalamus, rather than influencing a cortico-hippocampal control. However, this does not exclude the possibility that the cerebrum can change hippo-

campal activity if given the proper stimulus. It has long been known that the cingulate gyrus sends fibers to the hippocampus by way of the cingulate bundle.

Probably the most significant finding reported in the present study is the inverse activity of the cerebral cortex and hippocampus resulting from cerebellar stimulation. This is clearly shown in figures 1 and 3, where slow waves appear in the hippocampus, and low voltage fast waves appear in the cerebrum simultaneously. Quite the opposite patterns can be established quickly by electrical stimulation of the hippocampus. Slow waves appear in the cerebrum while low voltage fast waves appear in the hippocampus. Thus, by alternately stimulating the cerebellum and hippocampus, cortical activity can be driven toward either a low voltage fast activation-like pattern, or toward a slow wave pattern. In a well-responding animal it was possible to alternate these cortical rhythms many times during an hour.

In view of the cerebellar influences exerted upon the hippocampus, one might question what action (if any) does the hippocampus have upon the cerebellum. As can be seen in the above data, we were not able to demonstrate any changes except those that resulted from electrically-induced seizure activity in the hippocampus, becoming generalized and involving the cerebellum. It might be argued that this is somewhat surprising in view of widely accepted anatomical pathways, which could explain hippocampal-cerebellar transfer of activity. We refer to the well known hippocampal connections to the mammillary bodies via the fornix; the mammillotegmental tract and the tegmento-olivary system of fibers thence to the cerebellum. In the present experiments it did not appear to be an easy task to activate this multineuronal pathway. This is in keeping with the work of Green *et al.* (1953, 1954), showing that desirable as it might be to have a feedback system to the cerebellum, extensive hippocampal afterdischarges and seizure formation can occur in the absence of the cerebellum.

SUMMARY

Cerebello-hippocampal inter-relationships in the cat have been studied electrophysiologically.

1. The seizure characteristics of the hippocampus as described by Green and Shimamoto (1953) have been confirmed. Weak electrical pulses (usually 3-7 V. up to 1 mA. current flow) produce slow waves in the cerebrum, whereas stronger ones (usually over 7 V.) produce seizure patterns.

2. Cerebellar stimulation induces an activation pattern in the cerebrum, and synchronized slow waves in the hippocampus, cerebral activity can be changed from a low voltage fast activation-like tracing to slow waves and then back again. Such effects are readily blocked by barbiturate anesthesia.

3. Although the pathways used for interaction between these two structures have not been worked out, evidence is presented to show the possibility of involvement of the intralaminar thalamic nuclei.

4. Cerebellar stimulation can stop seizure patterns, and prolonged afterdischarges in the hippocampus which have been established by electrical stimulation.

RÉSUMÉ

Les inter-relations cérébello-hippocampiques du chat ont été étudiés au point de vue électro-physiologique.

1. Les caractéristiques paroxystiques de l'hippocampe, tels que décrits par Green et Shimamoto (1953), ont été confirmés. Des secousses électriques faibles (en général 3-7 V. jusqu'à un passage de courant de 1 milliampère) produisent des ondes lentes au cerveau, tandis que les secousses plus fortes (en général plus de 7 V.) produisent des tracés de type paroxystique.

2. La stimulation cérébelleuse induit un tracé d'activation dans le cerveau, et des ondes lentes synchrones dans l'hippocampe; l'activité cérébrale peut subir des changements d'un tracé de type voltage bas avec activation rapide à des ondes lentes, et inversement. L'anesthésie barbiturique bloque facilement les effets pareils.

3. Quoique les voies utilisées pour l'interaction entre ces deux structures n'ont pas été étudiées, on présente de l'évidence pour démontrer la possibilité de l'implication des noyaux thalamiques intralaminaires.

4. La stimulation cérébelleuse peut faire arrêter les tracés paroxystiques, ainsi que les après-décharges prolongées de l'hippocampe qui ont été établis par la stimulation électrique.

ZUSAMMENFASSUNG

Gegenseitige Beziehungen zwischen dem Kleinhirn und dem Ammonshorn wurden mit elektrophysiologischen Methoden bei der Katze untersucht.

1. Die durch Green und Shimamoto (1953) beschriebenen Characteristika von Ammonshornkrämpfen wurden bestätigt. Schwache elektrische Pulse (im allgeinen 3-7 Volt bis zu einer Stromstärke von 1 Milliampère) erzeugen langsame Wellen im Grosshirn, währenddem intensivere Reize (im allgemeinen über 7 Volt Spannung) Krampfentladungen produzieren.

2. Kleinhirnreizung produziert eine Aktivierungsantwort im Grosshirn gleichtzeitig mit synchronisierten langsamen Wellen im Ammonshorn, und die Grosshirnaktivität kann von einer niedergespannten raschen Aktivität, welche einer Aktivierungsantwort gleicht, zu einem langsamen Hirnstrombild verändert werden und wieder zurück zum ursprüglichen Typus. Diese Effekte können leicht durch Barbituratnarkose blockiert derden.

Obwohl die Verbindungen, über welche diese gegenseitigen Einflüsse vermittelt werden, noch nicht eruiert worden sind, so bestehen doch gewisse Anzeichen, dass möglicherweise die intralaminaren thalamischen Kerne an dieser Vermittlung beteiligt sind.

Kleinhirnreizung kann Krampfentladungen und langandauernde durch elektrische Reizung erzeugte Nachentladungen im Ammonshorn abstoppen.

REFERENCES

COOKE, P. M. and SNIDER, R. S. Some cerebellar effects on the electrocorticogram. *EEG Clin. Neurophysiol.*, **1953**, *5*: 563-569.

COOKE, P. M. and SNIDER, R. S. Some cerebellar influences on electrically-induced cerebral seizures. *Epilepsia*, Series III, **1955**, *4*: 19-28.

GREEN, J. D. and ARDUINI, A. A. Hippocampal electrical activity in arousal. *J. Neurophysiol.*, **1954**, *17*: 533-557.

GREEN, J. D. and SHIMAMOTO, T. Hippocampal seizures and their propagation. *Arch. Neurol. Psychiat.*, Chicago, **1953**, *70*: 687-702.

HASSLER, R. Uber Kleinhirnprojektion zum Mittelhirn und Thalamus beim Menschen. *Dtsch. z. Nervenheilkunde*, **1951**, *163*: 623-671.

KAADA, B. R. Somato-motor, autonomic and electrocorticographic responses to electrical stimulation of the rhinencephalic and other structures in primates, cat and dog. *Acta Physiol. Scand.*, **1951**, *83*: 1-263, *24*: Suppl.

LIBERSON, W. T. and AKERT, K. Hippocampal seizure states in guinea pig. *EEG Clin. Neurophysiol.*, **1955**, *7*: 211-222.

MORIN, F. and GREEN, J. D. Diffuse after-discharges following stimulation of the fimbria hippocampi. *Amer. J. Physiol.*, **1953**, *175*: 251-257.

RAND, R. W. An anatomical and experimental study of the cerebellar nuclei and their efferent pathway in the monkey. *J. Comp. Neur.*, **1954**, *101*: 167-224.

RANSON, S. W. and INGRAM, W. R. The diencephalic course and termination of the medial lemniscus and the brachium conjunctivum. *J. Comp. Neur.*, **1952**, *56*: 257-275.

ROSE, J. E. and WOOLSEY, C. N. Organization of the mammalian thalamus and its relationships to the cerebral cortex. *EEG Clin. Neurophysiol.*, **1949**, *1*: 391-404.

SCHOOLMAN, A. and DELGADO, J. M. R. Cerebrocerebellar relations in the awake cat. *J. Neurophysiol.*, **1958**, *21*: 1-16.

SNIDER, R. S. and STOWELL, A. Receiving areas of the tactile, auditory and visual systems in the cerebellum. *J. Neurophysiol.*, **1944**, *7*: 331-357.

WHITESIDE, J. A. and SNIDER, R. S. Relation of cerebellum to upper brain stem. *J. Neurophysiol.*, **1953**, *16*: 397-413.

Reference: IWATA, K. and SNIDER, R. S. Cerebello-hippocampal influences on the electroencephalogram. *EEG Clin. Neurophysiol.*, **1959**, *11*: 439-446.

PRINTED IN CANADA

STUDIES ON THE SUPRACALLOSAL MESIAL CORTEX OF UNANESTHETIZED, CONSCIOUS MAMMALS [1]

I. Cat. A. Movements elicited by electrical stimulation

JOHN R. HUGHES, Ph.D.

With the technical assistance of

JOHN A. MAZUROWSKI, B.S.

Department of Neurology, Meyer Memorial Hospital and Department of Neurophysiology, Buffalo Medical School, Buffalo, New York

(Received for publication: January 5, 1959)

INTRODUCTION

Few experimenters have systematically explored the entire supracallosal mesial cortex. The location of this area within the depths of the two hemispheres and the proximity of the superior sagittal sinus make a direct approach to this region relatively difficult. Autonomic responses have been well described (Smith 1945; summarized by Kaada 1951) from the mesial cortex, in particular the cingulate area. However, somatic movements have not been systematically investigated from the entire supracallosal mesial region of alert, conscious cats or monkeys. This paper, reported previously in preliminary form (Hughes and Mazurowski 1958a, 1958b), is the first of a series of studies on the mesial cortex and will emphasize the movements elicited by electrical stimulation in the unanesthetized cat. The term, supracallosal mesial cortex, refers to the entire mesial surface superior to the corpus callosum.

APPARATUS AND METHOD

Figure 1 shows the type of electrode assembly that was implanted onto the surface of the mesial cortex of cats. The operative procedure, performed with the use of Nembutal, included the removal of a narrow strip of bone along the midline, sufficient to expose the entire extent of the cortex under study. The dura was then cut slightly lateral to the superior sagittal sinus, which was gently retracted to expose the mesial cortex. The electrode assembly was placed so that it rested without pressure onto the mesial surface. The leads attached to the electrode assembly were

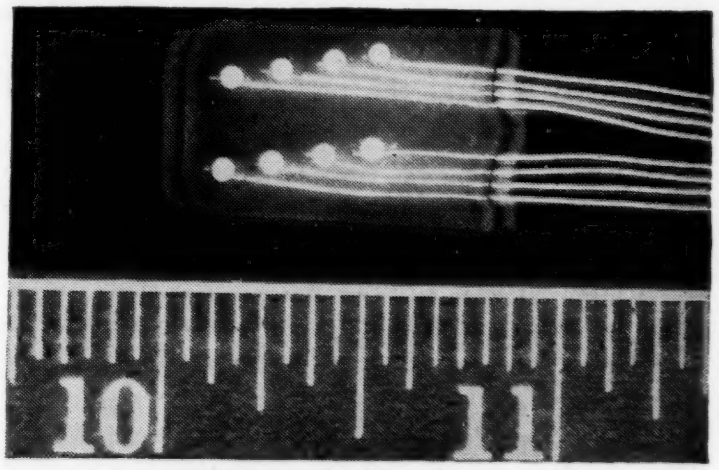


Fig. 1

The electrode assembly. Stainless steel electrodes (Type 316), 1-1.5 mm.^{2} in area, are embedded in a thin polyethylene sheet (0.5 mm. in thickness). These electrodes are exposed on one side of the sheet. Spot-welded to each electrode and embedded in the assembly are insulated stainless steel leads, 0.25 mm. in diameter, which are led through the skin of the neck. This assembly is implanted so that the electrodes rest without pressure onto one mesial cortical surface. The ruler shown in the figure is in inches.

secured in a tied loop of wire that passed between two small, closely-spaced holes in the skull. These leads were led through the skin of the neck where contact could be made with an alligator clip. A large stainless steel wire, serving as the diffuse current return, was

[1] This investigation was supported (in part) by a grant (B1564) from the National Institute of Neurological Diseases and Blindness and (in part) by a grant (39-16 I) from the American Cancer Society.

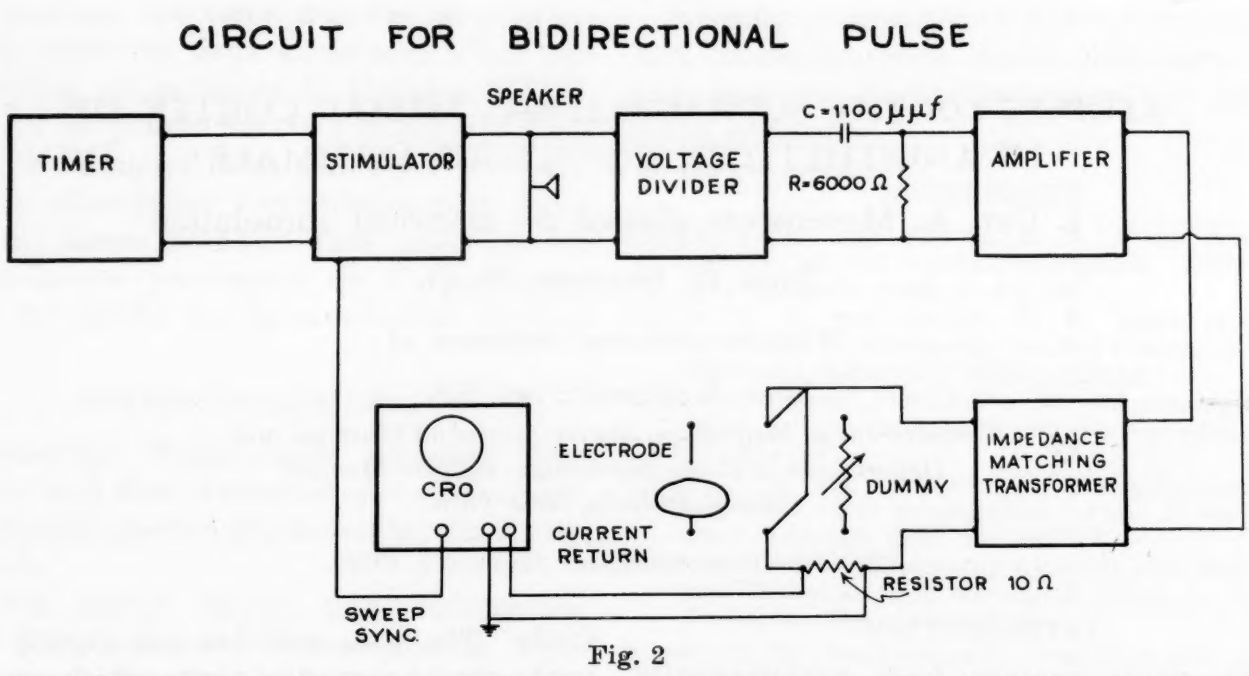


Fig. 2

Apparatus used for stimulation. The timer was set so that the train duration was always 5 sec. The RC circuit differentiated the rectangular pulse from the stimulator so that a bidirectional pulse resulted (see fig. 3). The resistance for each electrode was determined with each stimulation. This was done by setting the dummy variable resistance so that the current through it was equal to that through the electrode. The current was determined on the C.R.O. with each stimulation by converting the voltage drop across the 10 ohm resistor into current. The diffuse current return was a large stainless steel wire that was implanted over the outside periphery of the skull under the scalp.

implanted around the periphery of the skull and was led through the skin of the neck.

Figure 2 shows the apparatus used for stimulation (Lilly *et al.* 1955a) and in figure 3 the bidirectional stimulating pulse is seen. Evidence (Lilly 1955b) exists that this pulse can be considered relatively non-injurious; figure 4 shows that it separates well the thresholds for movement (lower) and electrical epileptiform after-discharge (higher)[1]. The peak current and the resistance were recorded with each stimulation. The train duration was always 5 sec.; usually 2-3 min. intervened between stimulus trains. The data reported in this study were collected only after full post-operative recovery, approximately 1-2 weeks after operation. The cats were completely free of all restraints and were trained for 1-2 weeks to lie quietly in a given position on the experimental table. The motor effects of the stimulation were directly observed by two experimenters. The results in this paper are based on data collected from 4 animals, each of whom served as experimental animals for as long as 6 months. Figure 5 shows the electrode positions that were studied; each

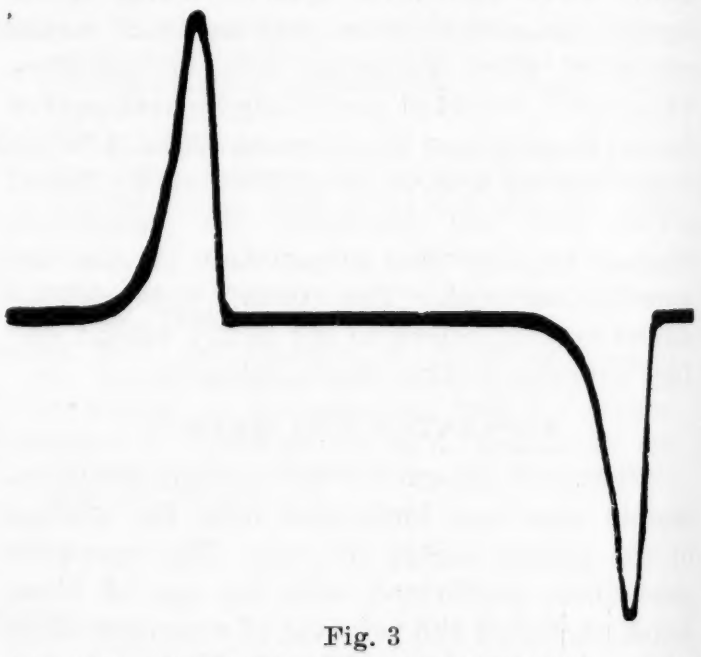


Fig. 3

The bidirectional pulse used for stimulation. A rectangular pulse, 200 micro-sec. in duration, was differentiated by an RC circuit so that a bidirectional pulse resulted. There was a separation of 200 μsec. between the positive and negative phases, each 60 μsec. in duration. The peak current of the positive pulse was determined with each stimulation.

[1] The author wishes to thank Dr. H. H. Jasper who advised an investigation of this point.

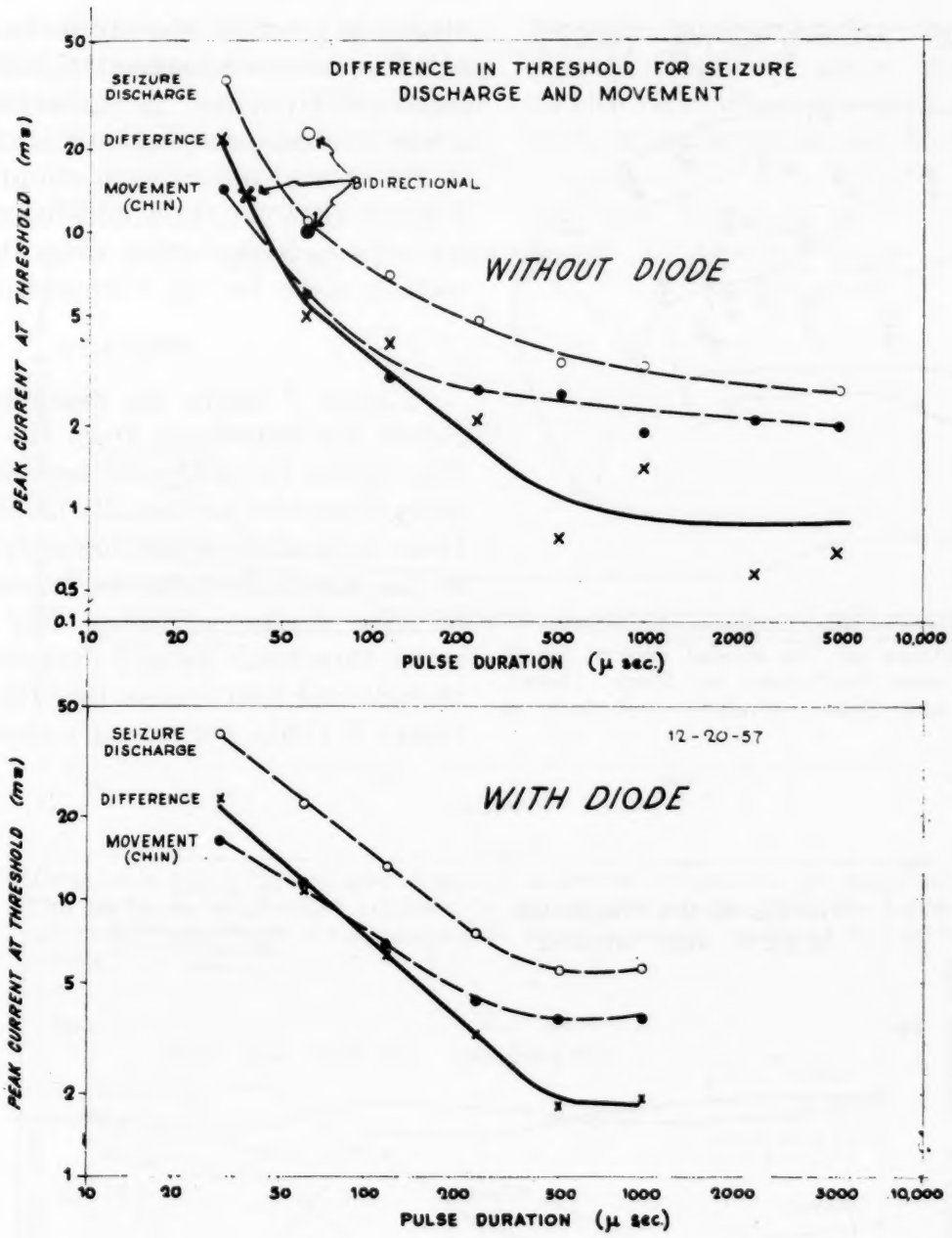


Fig. 4

Cat (Mary) 12-17-57 Rt. mesial cortex, unanaesthetized. Electrode 8. Differences in threshold for movement and seizure discharge with different stimulating pulses. The abscissa shows the duration (in micro-sec.) of unidirectional stimulating pulses and the ordinate shows the peak current at threshold in milliamperes. The frequency of stimulation is 90/sec. The threshold for movement (dots) is always lower than that for seizure discharge (open circles), an electrical epileptiform after-discharge, recorded on the EEG machine. The difference between these thresholds is shown by the solid line drawn as a best fit through the X's. Note that at the lower pulse durations the difference between the threshold for movement and seizure discharge may be as high as 20 mA.; at the longer pulse durations (greater than 1 msec.) this difference may be less than 1 mA. On the top graph the values are shown for the bidirectional stimulating pulse that is seen in figure 3. The two threshold values are shown at the 60 μsec. point on the abscissa, although the abscissa refers particularly to unidirectional pulses. The difference (X) between the two threshold values for the bidirectional pulse is shown on the appropriate ordinate value and is placed on the solid line drawn through the other X values. Note that this bidirectional pulse separates well the thresholds for movement and seizure discharge. The bottom graph shows similar, but less variable results using a germanium diode in the stimulating circuit in order to avoid any bidirectional component with the unidirectional stimulus.

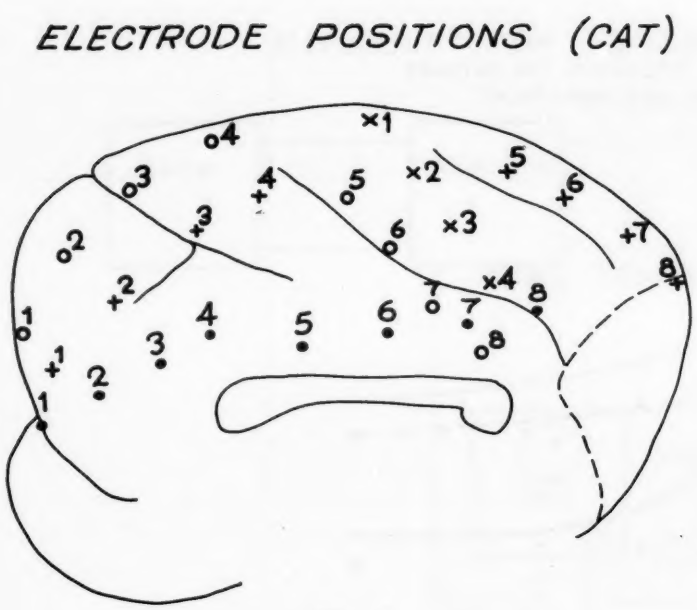


Fig. 5

The electrode positions on the mesial cortex (cat). Eight electrodes were implanted in Mary (dots), Sandy (crosses), and Spike (circles), and four in Willie (X's).

electrode position was studied at many different frequencies of stimulation from 1 to 1000 pulse-pairs per sec. A concerted attempt was made to maintain a given state of alertness in the animal before each stimulation. Figure 6 shows that the threshold for movement may be twice as high during sleep than during the waking state for all stimulating frequencies.

RESULTS

Figure 7 shows an example of threshold curves for movement from the mesial cortex. The curves for different movements from the same electrodes are usually more widely spaced from each other at the lower frequencies than at the higher frequencies, where they tend to be more similar in value. For a given movement, thresholds usually decrease at the higher stimulating frequencies (see fig. 8). However, figure 7 (chin curve, e.g.) shows that only a

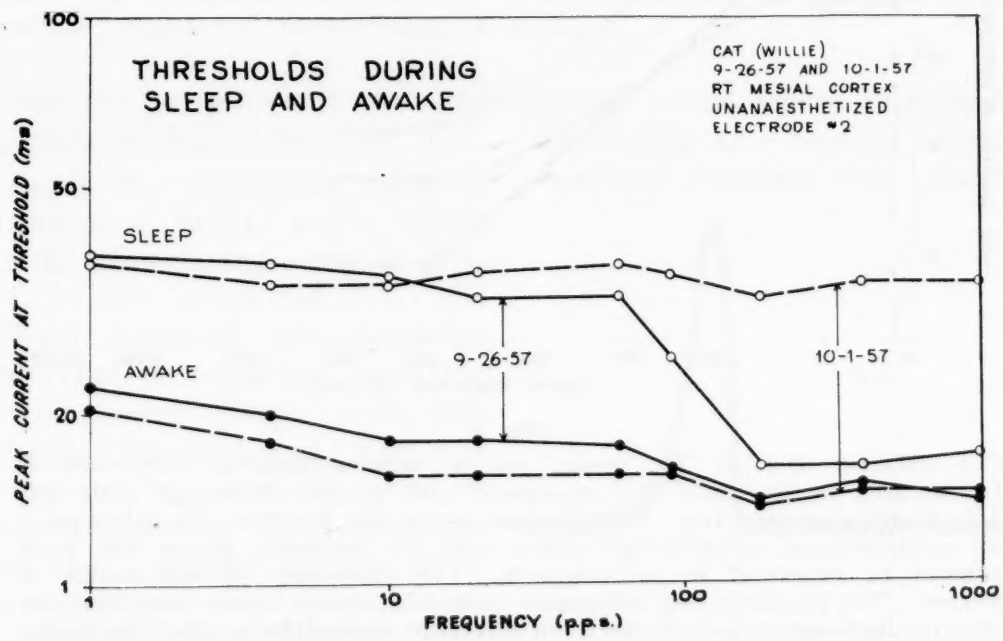


Fig. 6

Differences in threshold for movement during the states of sleep and wakefulness. The abscissa shows the frequency in pulse-pairs per second; the ordinate shows the peak current at threshold in milliamperes. On 9-26-57 the threshold for movement during sleep was approximately twice as high as that found during the waking state for all frequencies of stimulation, except for the higher frequencies. The impression at that time was that the higher frequencies tended to awaken the sleeping animal and, therefore, bring the two curves together. On 10-1-57 the same experiment was repeated except that the experimenters made more certain of a deep natural sleep. The thresholds during sleep are approximately twice as high as those found in the waking state for all frequencies of stimulation.

slight decrease in threshold may be related to the fact that the absolute value of these thresholds is relatively low. With higher thresholds there is usually a greater absolute decrease in threshold with increase in frequency. Figure 7 shows the responses from an electrode situated adjacent to the olfactory bulb; stimulation at any frequency from 1 to

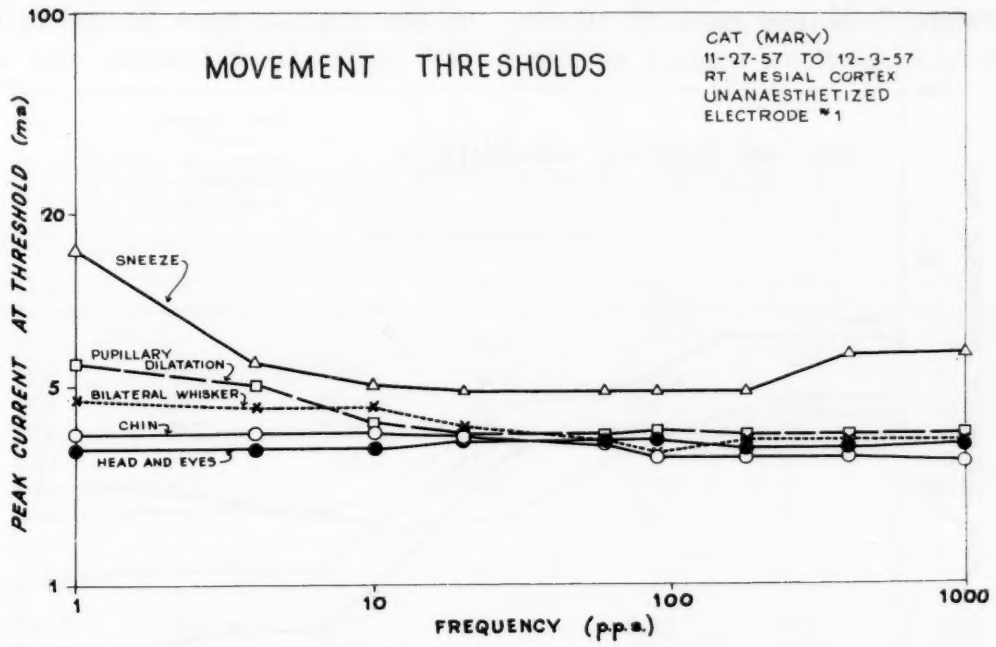


Fig. 7

Thresholds for different movements at different frequencies of stimulation. The electrode was located adjacent to the olfactory bulb. Note the sneezing response, which was indistinguishable from a sneeze produced by natural causes.

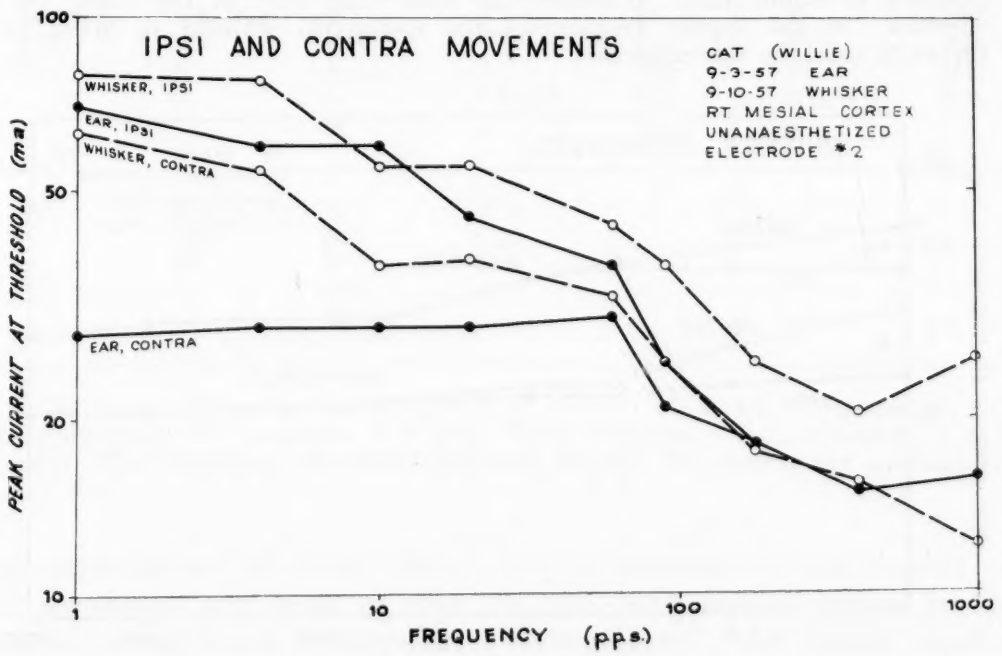


Fig. 8

Thresholds for ipsilateral and contralateral movements. For all frequencies the contralateral whisker is lower in threshold than the ipsilateral. The contralateral ear is lower in threshold than the ipsilateral for the lower frequencies of stimulation; at the higher frequencies, the threshold for contralateral and ipsilateral ear movement is the same.

1000 per sec. could elicit a sneeze indistinguishable from one produced by natural causes.

Ipsilateral and bilateral responses are frequently seen from stimulation of the mesial cortex; they comprise 31 per cent of all observed responses and 50 per cent of the responses that could be lateralized, excluding responses of the chin, anus, tail, etc. Figure 8 to 10 show threshold curves for bilateral and ipsilateral movements. The most common curve of this type is seen in figure 8 which shows

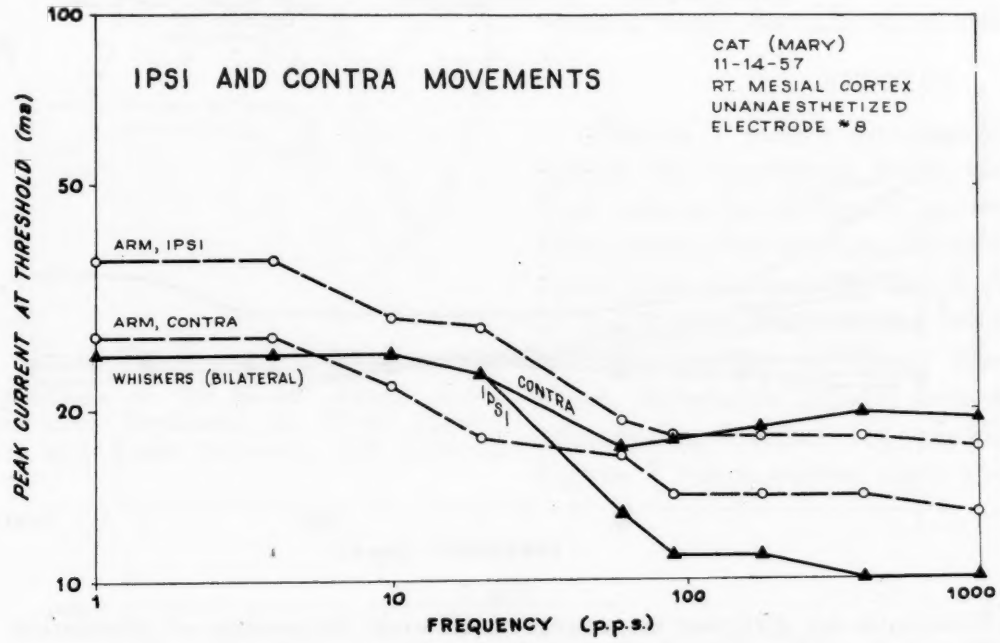


Fig. 9

Thresholds for ipsilateral and contralateral movements. Note that the contralateral arm is lower in threshold than the ipsilateral for all frequencies of stimulation. Whiskers are seen bilaterally at the lower frequencies; at the higher frequencies the ipsilateral whisker is lower in threshold than the contralateral.

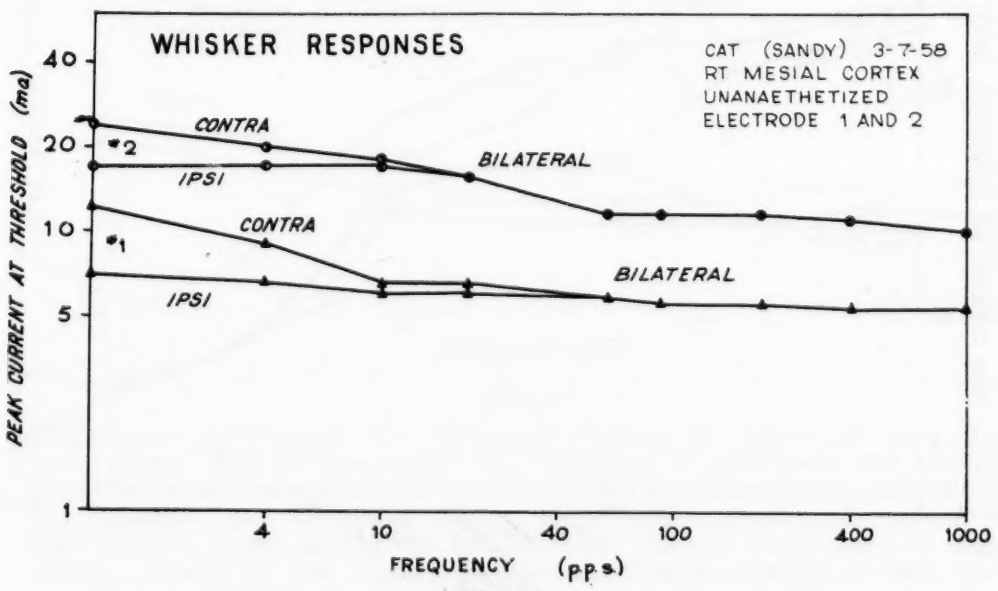


Fig. 10

Thresholds for ipsilateral and contralateral whisker responses. Note that at the lower frequencies the ipsilateral whisker response is lower in threshold than the contralateral for both electrodes # 1 and # 2. At higher frequencies the responses are bilateral.

the contralateral response lower in threshold than the ipsilateral at the lower frequencies and a bilateral response at the higher frequencies. At times, bilateral responses are seen at the lower frequencies but at the higher frequencies the ipsilateral response is lower in threshold than the contralateral (fig. 9). Conversely, from stimulation of other electrodes, bilateral responses are seen at the higher frequencies but at the lower frequencies the ipsilateral response is lower in threshold than the contralateral (fig. 10).

Table I shows the movements that are seen from each electrode with stimulation at 90/sec. Although responses of the extremities are clearly seen from some electrodes, the majority (86 per cent) of all observed responses involve the face and head.

Figure 11 shows the low threshold areas on the mesial cortex for various types of movements. The bilateral and ipsilateral responses are seen mainly in the posterior region. Figure 12 summarizes the results of stimulation of the cat's mesial cortex in the form of a "felunculus", the feline equivalent of the human homunculus. Two felunculi are shown: the anterior one, lower in threshold, is mainly contralateral in representation; the posterior one shows a front view of the face since ipsilateral and bilateral facial responses are pro-

TABLE I

MOVEMENTS FROM MESIAL CORTEX

	ELECTRODE No.							
	1	2	3	4	5	6	7	8
CAT: MARY	C HE Wb OO PD SN	C Wb OO HE PD SN	C Wb PD HE OO	PD HE L OO C Wb	C OOb Eb Wb PD HEi Lb	HEi C OOi Wi PD L E	Eb C HE OO Wb PD L	C,Wi Eb L OO Li HE W PD
SANDY	Wi,C Wb HE PD OOi	PD HE C,Wb	PD HE Wb OOb,LG C	T A LG PD HEi OO,Wb	HEi Wb,C Eb,OO PD HEi-HE	Wb C,E HEi,Eb PD,OO	HE PD Eb,Wb C,OO	HE Wb,C,N PD
SPIKE	Wb,HE PD C	HE,PD Wb N C	T PD A,LG L W	T TS A PD,LG L	Eb PD Wb HE LG	E PD Eb HE,Wb T	Eb PD HE Wb	Wb PD HE Eb L
WILLIE	W	E OOb W	E HE Wb PD OOb	Wb HE Eb PD				

A = anus, C = chin, E = ear, HE = head and eyes, L = elbow, LG = leg, N = nostril, OO = orbicularis oculi, PD = pupillary dilation, SN = sneeze, T = tail, TS = testicles, W = whiskers, i = ipsilateral and b = bilateral movement. The frequency of stimulation was 90/sec. Movements are contralateral unless otherwise indicated.

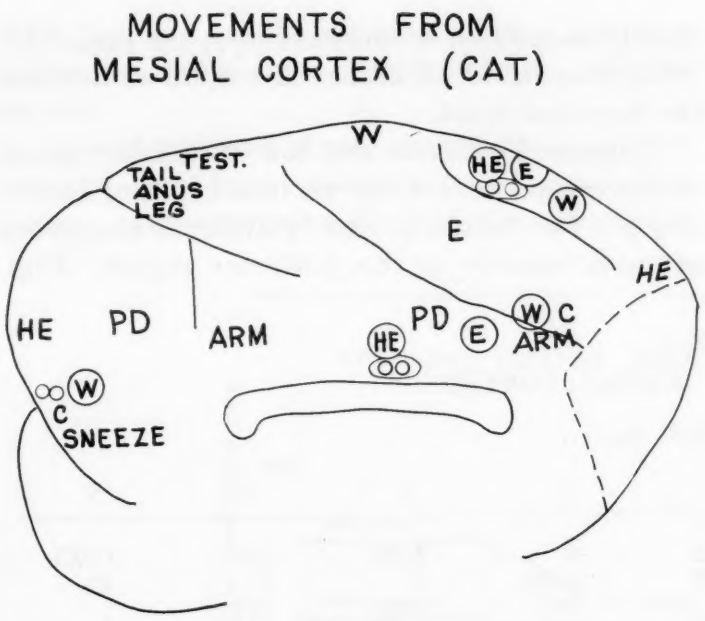


Fig. 11

Low threshold areas for different movements from the mesial cortex. C = chin, E = ear, HE = head and eye, OO = orbicularis oculi, PD = pupillary dilation, Test = testicules, W = whisker. The circled symbols indicate that the movements are ipsilateral and bilateral. The frequency of stimulation is 90/sec.

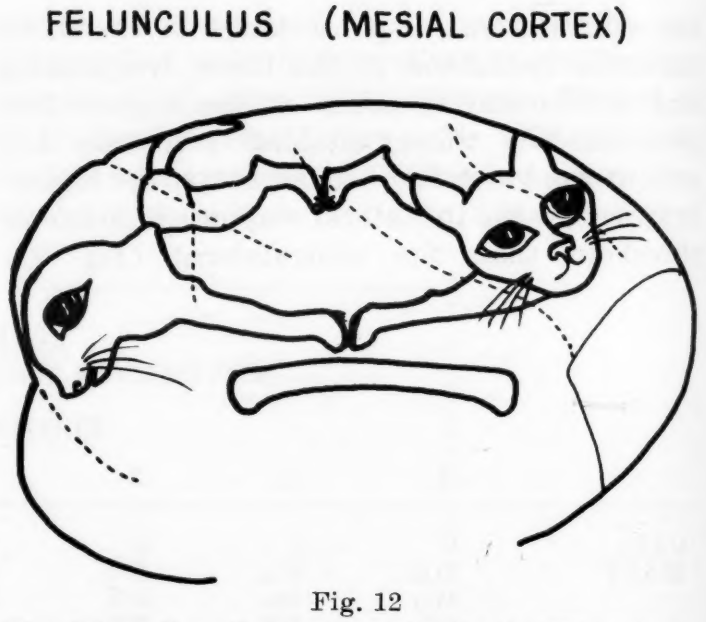


Fig. 12

Two felunculi on the mesial cortex (cat). The anterior felunculus, lower in threshold, has mainly a contralateral representation. No ear movement is found in this area. The posterior felunculus is shown with a front view of the face, because of the prominent ipsilateral and bilateral facial movements found in this region. The frequency of stimulation is 90/sec.

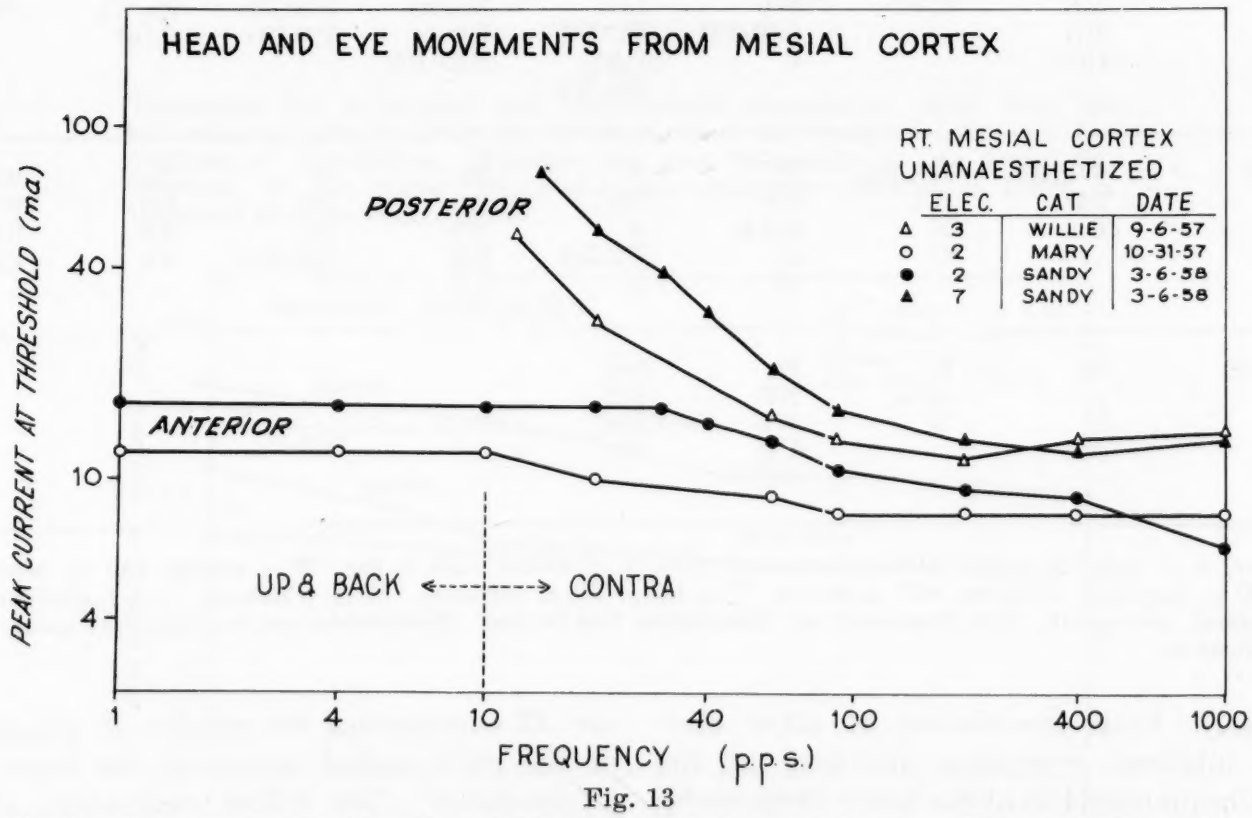


Fig. 13

Head and eye movements from the anterior and posterior mesial cortex. The results from four different electrode locations in three different cats are shown. Stimulation of the anterior region at the lower frequencies produces an up and back movement of the head and eyes; at the higher frequencies the movement is to the contralateral side. Stimulation of the posterior region produces contralateral responses without any up and back responses of the head and eyes. In the posterior region, low threshold values are seen only at the higher frequencies of stimulation.

minently represented. As previously stated, the majority of all observed responses involve head and facial movements and the regions yielding this type of response are not restricted to the area of the head and face shown on the felunculi. Figure 12 indicates only the relatively low threshold areas for the various movements. No ears are found on the anterior felunculus. No significant differences are found between the maps determined for the stimulating frequency of 90/sec. and 1/sec. The threshold curves seen in figure 13 indicate a difference between the anterior and posterior felunculus. In the anterior region, the head and eyes show up and back along with contralateral movements and respond to both the lower and the higher frequencies of stimulation. The posterior region produces contralateral responses without any up and back responses of the head and eyes. Relatively low threshold values are found only at the higher frequencies of stimulation. Not only for head and eye movements, but also for all other types of movements, the posterior felunculus shows low threshold values only at the higher stimulating frequencies. One exception is pupillary dilation. The anterior felunculus shows dilation with relatively low threshold values only at the higher frequencies of stimulation and the posterior felunculus shows a low threshold response both at the lower and higher frequencies.

DISCUSSION

One of the important features of this study is the concerted attempt to use a near-physiological preparation for the investigation of movements, elicited by stimulation of the cat's mesial cortex. A premium was placed upon the avoidance of injury: (1) thin, specially constructed electrode assemblies rested without pressure on the mesial surface; (2) a relatively non-injurious waveform was used for stimulation and separated well the thresholds for movement (lower) and seizure discharge (higher); (3) the experiments were performed on conscious, alert, unanesthetized animals; and (4) recordable data was collected only after full post-operative recovery of the animal. The use of electrical stimulation is obviously not physiological (Walshe 1957), but this technique has certainly proved useful in the investigation of motor functions of the cerebral cortex.

An attempt was made to achieve a given state of alertness in the animals during stimulation. Figure 6 shows the great difference in the threshold of movement for the sleeping and for the awake states. No evidence exists in this study to determine whether the locus of the effect of the sleeping state in raising the movement threshold is central or peripheral — the figure is presented as a methodological point.

The threshold values found in this study of the mesial cortex are within the same range as those found from stimulation of the lateral surface (Lilly and Hughes 1956). Stimulation of all electrodes from the anterior to the posterior portions of the mesial surface yielded specific movements. No "silent areas" were found, but the area between the two felunculi showed the highest threshold values. Thus, the function of the entire mesial cortex may include a motor representation. Other studies (Lilly, Hughes and Galkin 1956; Schneider and Crosby 1954) supply evidence that most, if not all, of the lateral surface of the cortex can produce some specific movement by electrical stimulation.

Previous studies (Dunsmore and Lennox 1950; Kaada 1951; Andy and Chinn 1951; and Kaada, Jansen and Anderson 1953) have referred to only a few somatic movements (mainly facial) elicited by stimulation of the cat's mesial surface. These latter studies most frequently involved the use of needle electrodes that penetrated into cortical tissue and thus produced damage. Also, unidirectional waveforms were used for electrical stimulation. In addition, the experimental animals were usually not in an alert and unanesthetized state after full post-operative recovery. It seems likely that the avoidance of injury retains a more physiological preparation and thus allows for more specific movements to be seen.

The data on the movements elicited by stimulation are probably best represented by

two felunculi (see fig. 12) with the two faces at the anterior and posterior portions of the mesial surface and the extremities in the middle. A recent study on monkeys (Showers and Crosby 1958) shows a pattern of movement on the anterior portion of the cingulate gyrus which repeats itself in reverse order on the posterior portion of this gyrus with the face represented at both ends. This evidence on the monkey is entirely consistent with the evidence in the present study represented by the felunculi in figure 12.

Although certain anatomical and functional subdivisions have been shown to exist within the mesial region, the form of the felunculi suggests that the supracallosal mesial cortex may be considered a relatively uniform part of the brain. No evidence was found, for example, to suggest that the cingular area includes any specific boundary or subdivision of motor representation. Although the supplementary motor area has been well described as part of the mesial cortex of the monkey (Woolsey *et al.* 1952) and of man (Penfield and Jasper 1954), the corresponding area in the cat remains uncertain. However, it seems possible that the anterior felunculus may be related to the supplementary motor area. The representation of the back leg, tail, anus and testicles of the anterior felunculus is located near the lateral surface of the cortex. The "classical" topographical distribution of these body parts in the monkey (Woolsey *et al.* 1952) and in man (Penfield and Jasper 1954) is located in a similar comparable region near the boundary between the mesial and lateral surfaces. Thus, it seems possible that this part of the anterior felunculus of the cat is directly related to, or may be actually part of the "primary" motor area that is seen mainly on the lateral surface but may extend onto the mesial surface.

Ipsilateral and bilateral movements are prominently represented on the posterior felunculus. The use of many different stimulating frequencies from 1 to 1000 per sec. is important in eliciting these movements. Figures 8 to 10 show that bilateral and ipsilateral movements may appear only at low frequencies of stimulation from some electrodes and only at high frequencies from others. Previously, only meager evidence existed for a prominent ipsilateral and bilateral representation on the mesial surface. Ipsilateral facial grimaces and bilateral movements of the extremities were described by Showers and Crosby (1958) from stimulation of the monkey's cingular gyrus. Strychninization of the anterior cingular gyrus in the cat and monkey (Dunsmore and Lennox 1950) produces discharges on both cortices and lesions in one supplementary motor area of monkeys (deVito and Smith 1958) produces bilateral neurological changes. Also, the latter experimenters showed that fibers from the mesial surface (supplementary motor area) project to both ipsilateral and contralateral motor area 4. This evidence supplies at least one possible neuroanatomical basis for bilateral and ipsilateral representation on the mesial cortex of monkeys. It seems possible that a similar neuroanatomical basis exists in the cat but clear evidence on this point awaits future experimentation.

SUMMARY

1. The supracallosal mesial cortex of alert, unanesthetized cats was stimulated by bidirectional pulses and mapped for movement.

2. The bidirectional pulse separates well the thresholds for movement (lower) and electrical epileptiform after-discharge (higher). An increase in the pulse duration of a unidirectional pulse brings these two thresholds closer together.

3. The threshold for movement during the sleeping state is approximately twice as high as that found during the waking state for all frequencies of stimulation.

4. Two "felunculi" (feline equivalent of homunculus) are found: the anterior felunculus has a lower threshold than the posterior one. The face is represented at the anterior and posterior portion of the mesial region with the extremities in the middle. The majority (86 per cent) of all observed responses from the mesial cortex involve movements of the face and head.

5. Ipsilateral and bilateral responses are prominently represented on the posterior felunculus.

6. Evidence is shown to suggest that functions of the entire supracallosal mesial cortex of the cat may include a motor representation.

RÉSUMÉ

1. Le cortex médian et supracalleux de chats éveillés a été stimulé par des influx bidirectionnels et la distribution du mouvement enregistré sur carte.

2. L'influx bidirectionnel sépare bien les seuils de mouvement (moins élevé) de la décharge épileptiforme (plus élevé). L'augmentation de la durée pulsatile d'influx unidirectionnel rapproche ces deux seuils.

3. Le seuil de mouvement pendant le sommeil est approximativement deux fois plus élevé qu'à l'état de veille pour toutes les fréquences de stimulation.

4. On trouve deux ''felunculi'' (équivalent félin l'homunculi) : l'antérieur a un seuil moins élevé que le postérieur. La face est représentée aux parties antérieure et postérieure de la région médial, les extrémités se trouvant à la partie moyenne. La majorité des réponses (86 pour cent) obtenues du cortex médian intéressent les mouvements de la face et de la tête.

5. Les réponses ipsilatérales et bilatérales sont représentées d'une manière proéminente sur le felunculi postérieur.

6. L'évidence présentée suggère que les fonctions du cortex médian supracalleux du chat peuvent comprendre une représentation motrice.

ZUSAMMENFASSUNG

1. Die supra-calloese mediale Hirnrinde einer wacher, nicht anaesthesierten Katze wurde mit richtungweschselnden Stromstössen gereizt und die Reaktionen aufgezeichnet.

2. Der richtungwechselnde Stromstoss trennt gut die Reizschwelle für Bewegungen (niedriger) und epileptiformer Nachentladungen (höher). Eine Zunahme der Impulsdauer eines gleichgerichteten Stromstosses bringt diese beiden Schwellenwerte einander näher.

3. Die Reizschwelle für eine Bewegung im Schlafzustand ist ungefähr doppelt so hoch wie im Wachzustand. Dies gilt für alle Reizfrequenzen.

4. Zwei ''Felunculi'' (Katzen-equivalent von Homunculus) wurden gefunden: Der anteriore Felunculus hat eine niedrigere Reizschwelle als der posteriore. Das Gesicht ist im anterioren und posterioren Teil der medialen Region, mit den Extremitaeten in der Mitte liegend, lokalisiert. Die Mehrzahl (88 Prozent) aller beobachteten Reaktionen des medialen Cortex sind Bewegungen des Gesichts und Kopfes.

5. Ipsilaterale und bilaterale Reaktionen sind vorwiegend im posterioren Felunculus represäntiert.

6. Die Wahrscheinlichkeit, dass die Funktionen des gesamten medialen supracallösen Kortex der Watze ein motorisches Gebiet einschliess, wird aufgezeigt.

REFERENCES

ANDY, O. J. and CHINN, R. M. Cingulate gyrus seizure. *Neurol.*, **1957**, *7*: 56-68.

DEVITO, J. L. and SMITH, O. A. Anatomical analysis of the supplementary motor area. *Fed. Proc.*, **1958**, *17*: 35.

DUNSMORE, R. H. and LENNOX, M. A. Stimulation and strychninization of supracallosal anterior cingulate gyrus. *J. Neurophysiol.*, **1950**, *13*: 207-213.

HUGHES, J. R. and MAZUROWSKI, J. A. Exploratory studies on the parasagittal mesial cortex of conscious, unanesthetized cats. *EEG Clin. Neurophysiol.*, **1958**a, *10*: 363.

HUGHES, J. R. and MAZUROWSKI, J. A. Parasagittal mesial cortex of conscious, unanesthetized cats. *Fed. Proc.*, **1958**b, *17*: 75.

KAADA, B. R. Somato-motor, autonomic and electrocorticographic responses to electrical stimulation of ''rhinencephalic'' and other structures in primates, cat and dog. *Acta physiol scand.* (Suppl. 83), **1951**, *24*: 1-285.

KAADA, B. R., JANSEN, J. and ANDERSON, P. Stimulation of the hippocampus and medial cortical areas in unanesthetized cats. *Neurol.*, **1953**, *3*: 844-857.

LILLY, J. C. and HUGHES, J. R. Unpublished results, **1956**.

LILLY, J. C., HUGHES, J. R., ALVORD, E. C. and GALKIN, T. W. Brief noninjurious electric waveform for stimulation of the brain. *Science*, **1955**a, *121*: 468-469.

LILLY, J. C., HUGHES, J. R., GALKIN, T. W. and ALVORD, E. C. Production and avoidance of injury to brain tissue by electrical current at threshold values. *EEG Clin. Neurophysiol.*, **1955**b, *7*: 458-459.

LILLY, J. C., HUGHES, J. R. and GALKIN, T. W. Some evidence for gradients of motor function in the whole cerebral cortex of the unanesthetized monkey. *XX International Cong. of Physiol.*, **1956**, 567-568.

PENFIELD, W. and JASPER, H. *Epilepsy and the Functional Anatomy of the Human Brain.* Little, Brown, and Co., Boston, **1954**.

SCHNEIDER, R. C. and CROSBY, E. C. Stimulation of second motor areas in the macaque temporal lobe. *Neurol.* **1954**, *4* (8): 612-622.

SHOWERS, M. J. C. and CROSBY, E. C. Somatic and visceral responses from the cingulate gyrus. *Neurol.*, **1958**, *8* (7): 561-565.

SMITH, W. K. The functional significance of the rostral cingular cortex as revealed by its responses to electrical excitation. *J. Neurophysiol.*, **1945**, *8*: 241-255.

WALSHE, F. M. R. States of consciousness in neurology. (First International Congress of Neurological Sciences) *Acta Medica Belgica*, **1957**, 141-145.

WOOLSEY, C. N. et al. Patterns of localization in precentral and supplementary motor area and their relation to the concept of a premotor area. ARNMD, **1952**, *30*: 328-264.

Reference: HUGHES, J. R. Studies on the supracallosal mesial cortex of unanesthetized, conscious mammals. I. Cat. Movements elicited by electrical stimulation. *EEG Clin. Neurophysiol.*, **1959**, *11*: 447-458.

PRINTED IN CANADA

STUDIES ON THE SUPRACALLOSAL MESIAL CORTEX OF UNANESTHETIZED, CONSCIOUS MAMMALS [1]

I. Cat. B. Electrical activity

JOHN R. HUGHES, Ph.D.

With the technical assistance of

JOHN A. MAZUROWSKI, B.S.

Department of Neurology, Meyer Memorial Hospital and Department of Neurophysiology, Buffalo Medical School, Buffalo, New York

(Received for publication: January 5, 1959)

INTRODUCTION

Few studies have featured recording from the supracallosal, mesial cortex of the conscious, alert, unanesthetized cat. The type and the character of the electrographic and clinical seizure pattern have not been systematically investigated for the mesial cortex. The neuroanatomical connection via the cingulum between the limbic region and the deep temporal structures, like the hippocampus, suggests that a psychomotor component may be evident in the clinical seizures originating in the limbic area. Aside from an investigation of the seizure activity of the mesial cortex, this study was designed to investigate certain features of other electrographic phenomena, such as photic driving, sleep spindles and a response resembling the K-complex of man.

METHOD

The electrode assembly, the type of surgical operation performed, the apparatus used for stimulation, the bidirectional type of stimulating pulse, and electrode positions tested on the mesial surface of the cat are all described under Apparatus and Method in the previous paper in this journal (page 447). The train duration of each stimulation was always 5 sec. Within 1-1.5 sec. after the end of intensive electrical stimulation, seizure activity was recorded on an 8-Channel Grass (Model III A) EEG machine from both the mesial and lateral surface of the cortex. The electrodes used on the lateral surface were similar to those used on the mesial surface. No distinction is made in this paper between seizure activity and (epileptogenic) afterdischarge. When full-blown clinical seizures occurred (46 were analyzed), the animal was usually held very firmly by the experimenters so that little movement artifact was recorded on the EEG machine. At times, the animal was permitted to move freely after the stimulation so that 16 mm. movies could be taken of the clinical seizure pattern. The number of electrographic seizures that were analyzed totaled 597. Although the results to be presented are based on data from four different cats, many of the figures are taken from the data on the cat, Mary, who was representative of all four cats. A Grass photic stimulator (Model PS-1) was used in the experiments involving photic driving.

The term, supracallosal mesial cortex, will refer to the entire mesial surface superior to the corpus callosum. The term, limbic cortex, will refer to the projection of the anterior thalamic nuclei onto the mesial surface and is divided into two parts: (1) the anterior limbic area, including (approximately) the cortex between the anterior third of the corpus callosum and the mesial extension of the cruciate sulcus, and (2) the posterior limbic area, including (approximately) the cortex between the posterior two-thirds of the corpus callosum and the splenial sulcus (after Rose and Wool-

1 This investigation was supported (in part) by a grant (B1564) from the National Institute of Neurological Diseases and Blindness and (in part) by a grant (39-16 I) from the American Cancer Society.

sey 1948). The posterior limbic area consists mainly of the cingular cortex, but also includes the retrosplenial area.

RESULTS

1. *Seizure discharges*

Short-termed electrographic seizure activity from the mesial cortex (lasting 5-10 sec.) is usually rhythmical and synchronized in form, except from the precentral agranular area and orbitofrontal region where desynchronized patterns are frequently seen. Rhythmical frequencies of 16-20/sec. are commonly seen from the suprasplenial gyri; frequencies of 26-28/sec. are noted from the posterior limbic area and frequencies of 16-18/sec. are seen especially from the anterior limbic area. Occasionally, the discharges from the anterior limbic area include a subharmonic frequency of 8-9/sec., as seen in figure 1. In a review of the instances when this halving phenomenon occurred, featuring the frequency of 8-9/sec., there was a marked tendency for its appearance after numerous stimulations eliciting many seizure discharges from a given area. Figures 2 and 3 show that after considerable epileptogenic activity has been elicited within a 1, 3 or 8-day period, seizure discharges show an increase in the slower frequencies of 8-9/sec., a decrease in the amount of faster frequencies of 16-18/sec., and an increase in threshold. These changes are probably related to the eliciting of seizure discharges, rather than to the stimulation itself, since no changes are noted with numerous stimulations at current values subthreshold to that yielding seizure discharges.

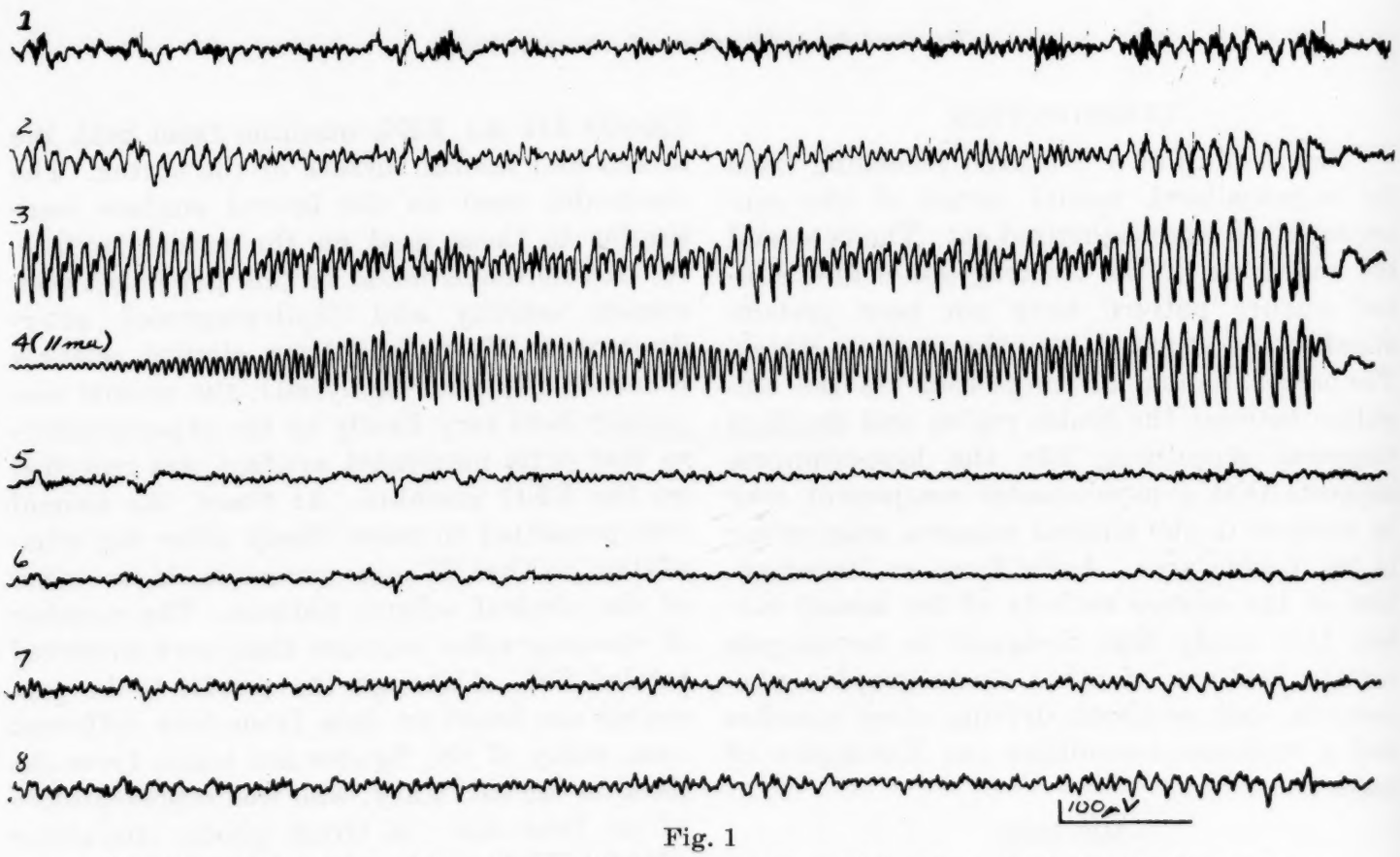


Fig. 1

Short-termed electrographic seizure activity from the mesial cortex (anterior limbic area). Electrode 4 of cat, Mary, was stimulated with 11 mA. for 5 sec. to elicit the seizure activity seen on electrodes 1-4. Note on electrode 4 the faster rhythmical frequency of 16-18/sec., followed by the slower subharmonic frequency of 8-9/sec.

Full blown, clinical and electrographic seizures of the limbic area lasting 1-2 min., begin with rhythmical activity like that seen in figure 1, but after 10-20 sec., feature high amplitude spike and wave-like complexes at 2-3/sec., as seen in figure 4. These seizures, elicited by intensive electrical stimulation, spread to the hippocampus. If the origin of the seizure is the posterior limbic area, the latency of the

spread to the hippocampus is usually 4-6 sec. If the origin is the anterior limbic area, the latency of spread may be as long as 20-30 sec. Seizure activity is not usually seen on the lateral surface unless a grand mal type of clinical seizure develops, as seen in figure 5. The

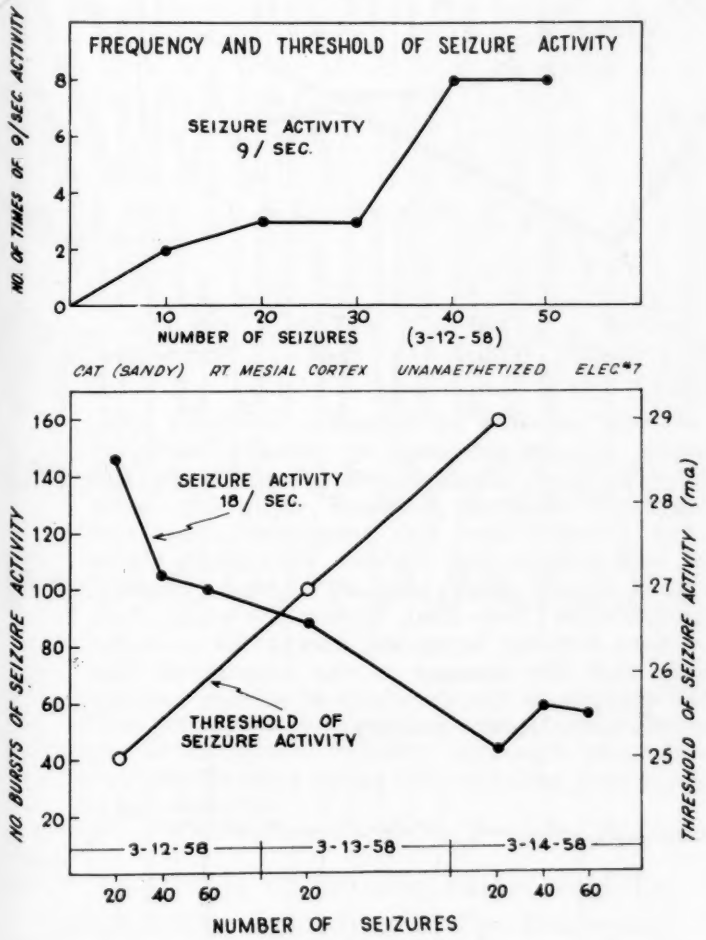


Fig. 2

Change in frequency and the threshold of seizure activity (elicited by intensive electrical stimulation), associated with short-termed electrographic seizures produced by periodic, electrical stimulation for one day (top) and three days (bottom) on the anterior limbic area. The top graph shows an increase in the number of times that the (slower) 9/sec. seizure activity is seen in each successive group of 10 electrographic seizures produced within one day. The bottom graph shows a decrease in the number of bursts of (faster) 18/sec. seizure activity that is seen in each successive group of 20 electrographic seizures produced within a period of 3 days. The bottom graph also shows an increase in the threshold of seizure activity to electrical stimulation within those 3 days.

seizures that appear restricted to the cortical limbic area, spreading to the hippocampus but not seen well on the lateral surface, are psychomotor-like in character. The prominent feature of these seizures is violent, wild running behavior, lasting longer than a minute. Also seen are pupillary dilation, urination and defecation, piloerection, chewing, licking and cleaning behavior. These seizures typically terminate with voracious eating, which became so predictable in one animal (Mary) that, at times, its daily feeding schedule consisted entirely of plans for 2-3 of these full-blown psychomotor-like seizures. Intensive electrical stimulation of the mesial surface outside the anterior and posterior limbic areas tends to elicit a grand mal type of seizure.

2. *Photic responses*

Photic driving of relatively high amplitude is seen on the mesial surface, as shown in figure 6. This figure shows that at certain flash frequencies, photic responses on the mesial surface may be nearly as high in amplitude as those on the lateral gyrus of the lateral surface. However, analysis of oscilloscopic traces shows that the latency of onset of the evoked visual response is 11-12 msec. from the lateral gyrus of the lateral surface and 14-16 msec. from the splenial gyrus of the mesial surface. The frequency of 5/sec. produces driving of highest amplitude on the mesial surface. Numerous recordings of the resting state of the cat showed that this same frequency of 5/sec. appears as the dominant frequency in the background rhythm for most of the mesial surface. Although considerable variability is seen from one electrode to another, it appears that the frequencies producing the best driving are multiples of five. The highest frequency that produces clear photic driving is approximately 50/sec.

Figure 7 shows that driving of highest amplitude at 5/sec. is seen on the splenial gyrus, rather than the suprasplenial gyrus which shows the highest amplitude of photic responses at 1/sec. An area within both the splenial and suprasplenial gyri shows driving of highest amplitude at photic frequencies of 15-17/sec. and 25-30/sec. The different outlined areas on the posterior mesial surface shown in figure 7 were determined on the basis of at least 150 measurements at each frequency of photic stimulation. The area on the posterior mesial surface showing the

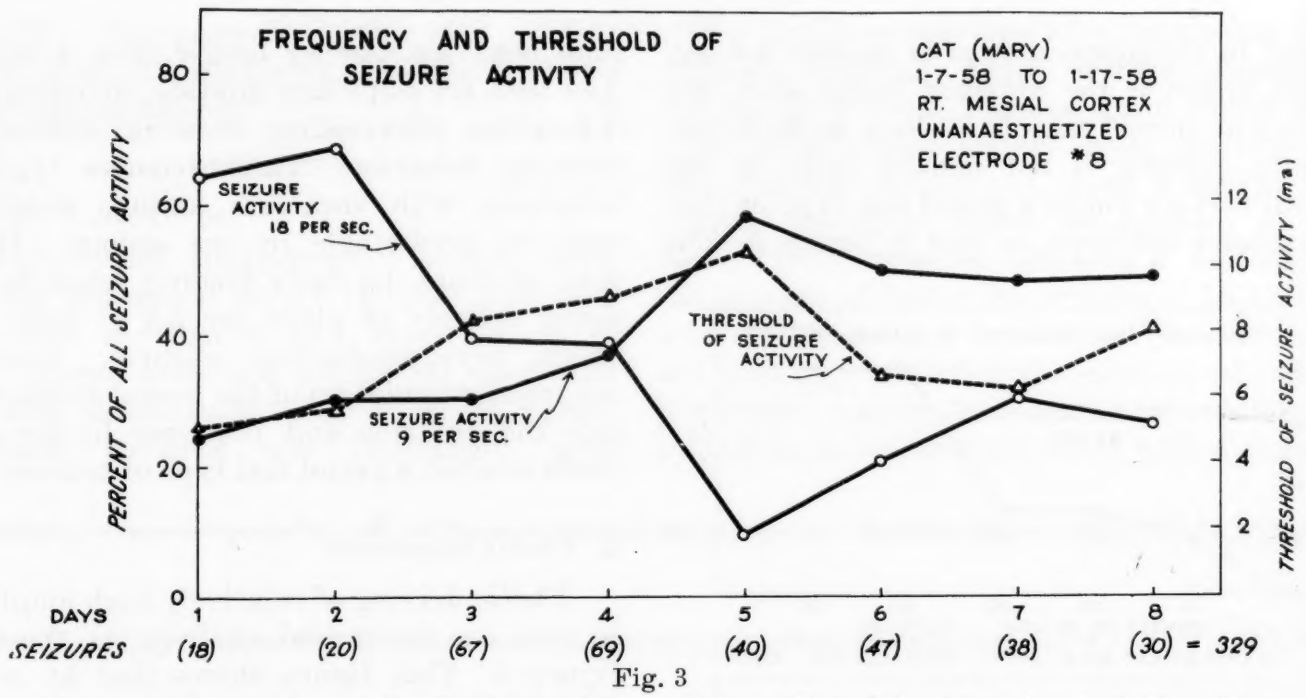


Fig. 3

Change in frequency and threshold of seizure activity (elicited by intensive electrical stimulation), associated with short-termed electrographic seizures produced by periodic, electrical stimulation for eight days. On the abscissa the 8 days of stimulation are represented and also (in parentheses) the number of electrographic seizures produced each day. For calculation, the frequency of seizure activity was grouped into five categories: less than 9/sec., 9/sec., between 9/sec. and 18/sec., 18/sec., and greater than 18/sec. This graph shows the number of times that seizure activity is seen at 9/sec. (dots) and at 18/sec. (circles), calculated in terms of the percent of all seizure activity. Note that during the eight days of stimulation the amount of (slower) 3/sec. seizure activity increases, except for a slight reversal toward the end of the experiment. Note that the changes in the amount of this (slower) 9/sec. activity are directly related to the changes in the threshold of seizure activity and are inversely related to the changes in the (faster) 18/sec. activity.

Fig. 5

Same as figure 4, except 90 sec. later. Note that the lateral surface (channel 1 and 2) now shows seizure activity, although some movement artifact is included. The limbic area continues to show spike and wavelike complexes. Clinically, the seizure at this time is grand mal in character.

highest amplitude of driving varies slightly, but significantly, according to the frequency of the stimulation. However, it should be emphasized that clear photic driving is seen at one time or another from all the electrodes from the anterior to posterior tip of the mesial surface.

3. *Responses during natural sleep*

Figure 8 shows the electrographic response to a hand-clap during a drowsy state in the cat. This response, appearing prominently on the mesial surface and resembling the K-complex in man, is best seen during the spindle state of sleep and is not easily elicited during states of deep natural sleep. The form of the response varies, but usually consists of a prominent negative, followed by a longer-lasting positive slow wave complex. At times, a diphasic sharp wave precedes the slow negativity. Tests of repeated hand-claps show that the excitability cycle is approximately 2-3

Fig. 4

Seizure activity in the full-blown clinical and electrographic seizure of the cat's limbic area (Mary). The first two channels show activity from the middle suprasylvian gyrus of the lateral surface (calibration of 400 μV. represented on the upper right). The last 6 channels show activity from the ipsilateral limbic area of the mesial surface (calibration of 400 μV. represented on the lower right). This figure shows the activity of the lateral and mesial surfaces 30 sec. after a seizure was induced by stimulation of electrode 3 (channel 5) with 35 mA. Note the high amplitude spike and wavelike complexes at 2-3 sec. seen on the first 4 electrodes of the limbic area with little evidence of seizure activity on the lateral surface (channels 1 and 2). Except for the onset of seizure activity (usually similar to that seen in figure 1), the mesial surface, especially the limbic area, shows spike and wavelike complexes throughout the entire electrographic and clinical seizure. Clinically, the seizures at this time are psychomotor-like in character.

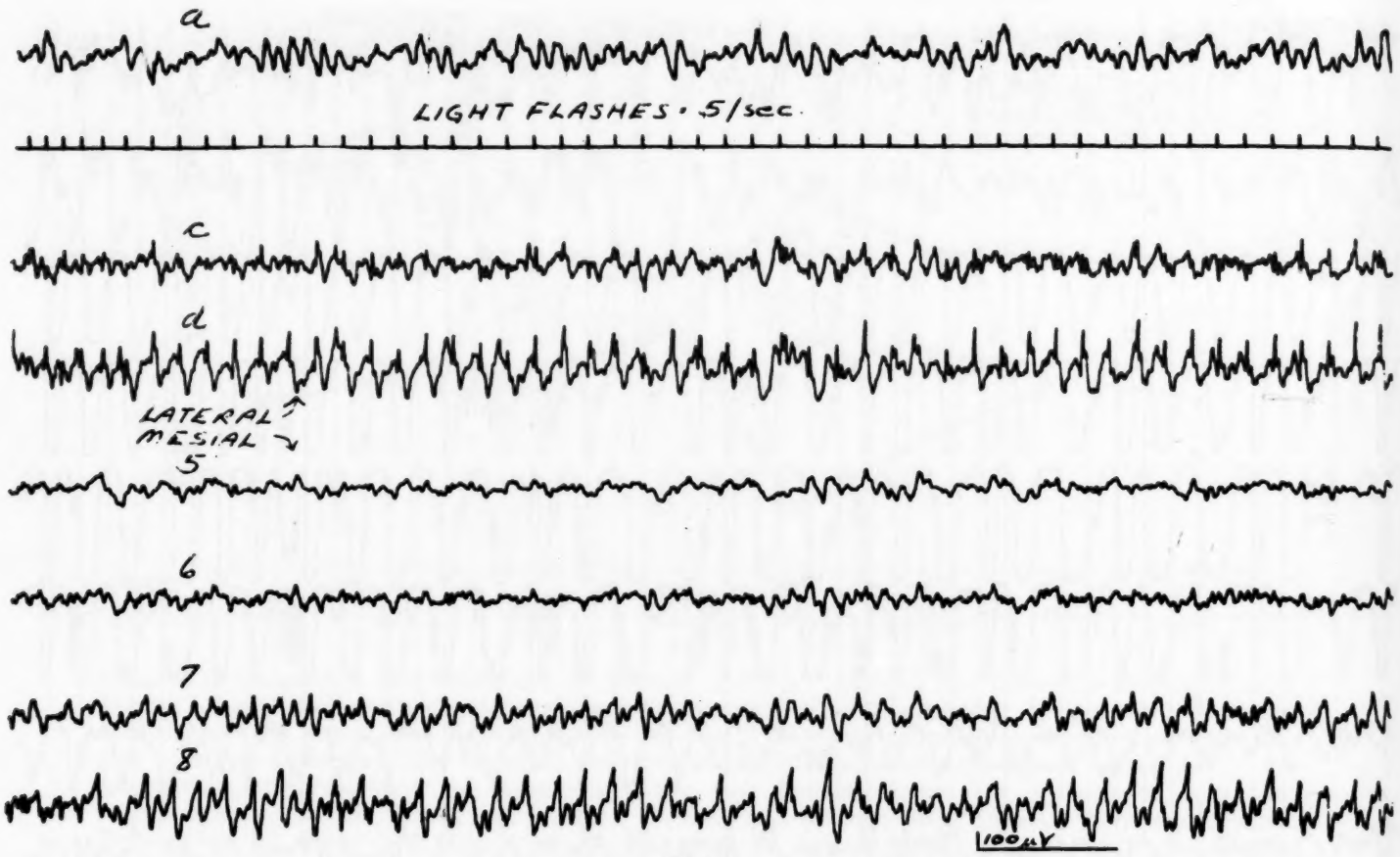
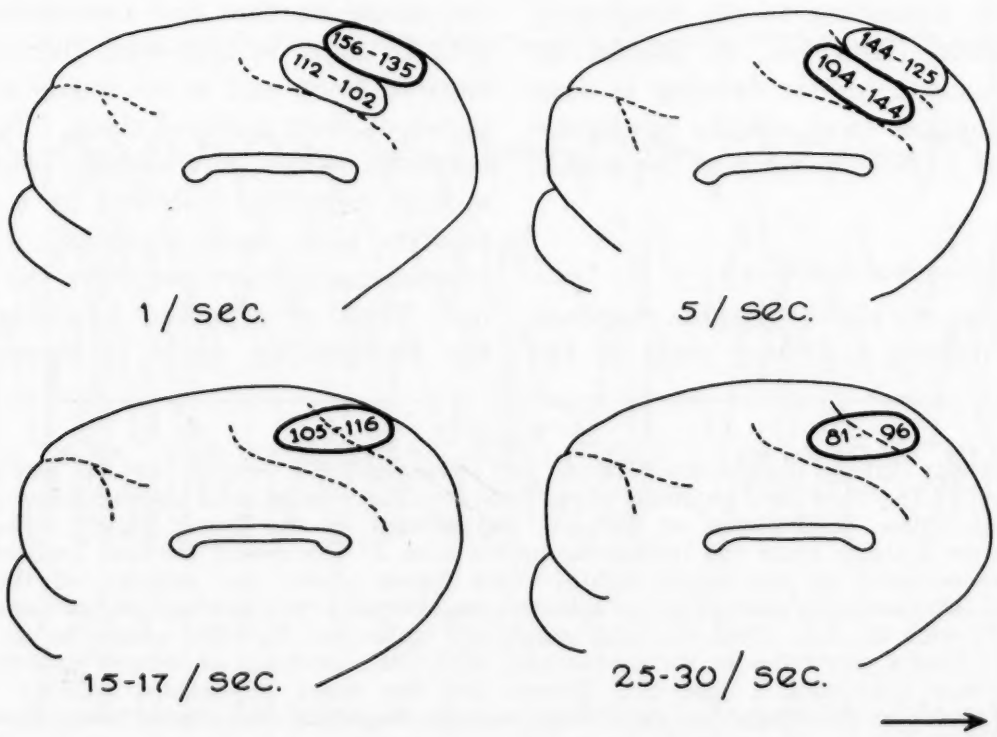


Fig. 6

Photic driving recorded from the lateral and mesial cortex of the cat (Mary). Channel 1 shows activity from the middle suprasylvian gyrus (a) and channels 3 and 4 from the lateral gyrus (c and d) of the lateral surface; channels 5-8 show activity from the posterior mesial surface. Channel 2 monitors the light flashes at 5/sec. Note the photic driving of relatively high amplitude on both the lateral and mesial cortex.



sec., since a diminished amplitude of response is seen if stimuli are presented more frequently than every 2-3 sec. Acoustic stimuli are the most effective in producing this response, which can be elicited less easily by tactile stimuli. Similar responses, appearing spontaneously, are frequently seen. Figure 8 shows that there may be a transient slowing of the heart rate for a few seconds following this response. Analysis of at least 50-60 beats before and after 55 K-complexes showed that slowing of the heart beat is seen with 56 per cent of the responses to a hand-clap and with 24 per cent of the spontaneous responses.

Figure 9 (bottom) shows that the maximal amplitude of this response resembling the K-complex appears on the anterior limbic area. The amplitude of the response usually measures, on the average, 350 μV. within this region. The top of figure 9 shows that the maximal amplitude of spindle bursts is seen also within the anterior limbic region. In

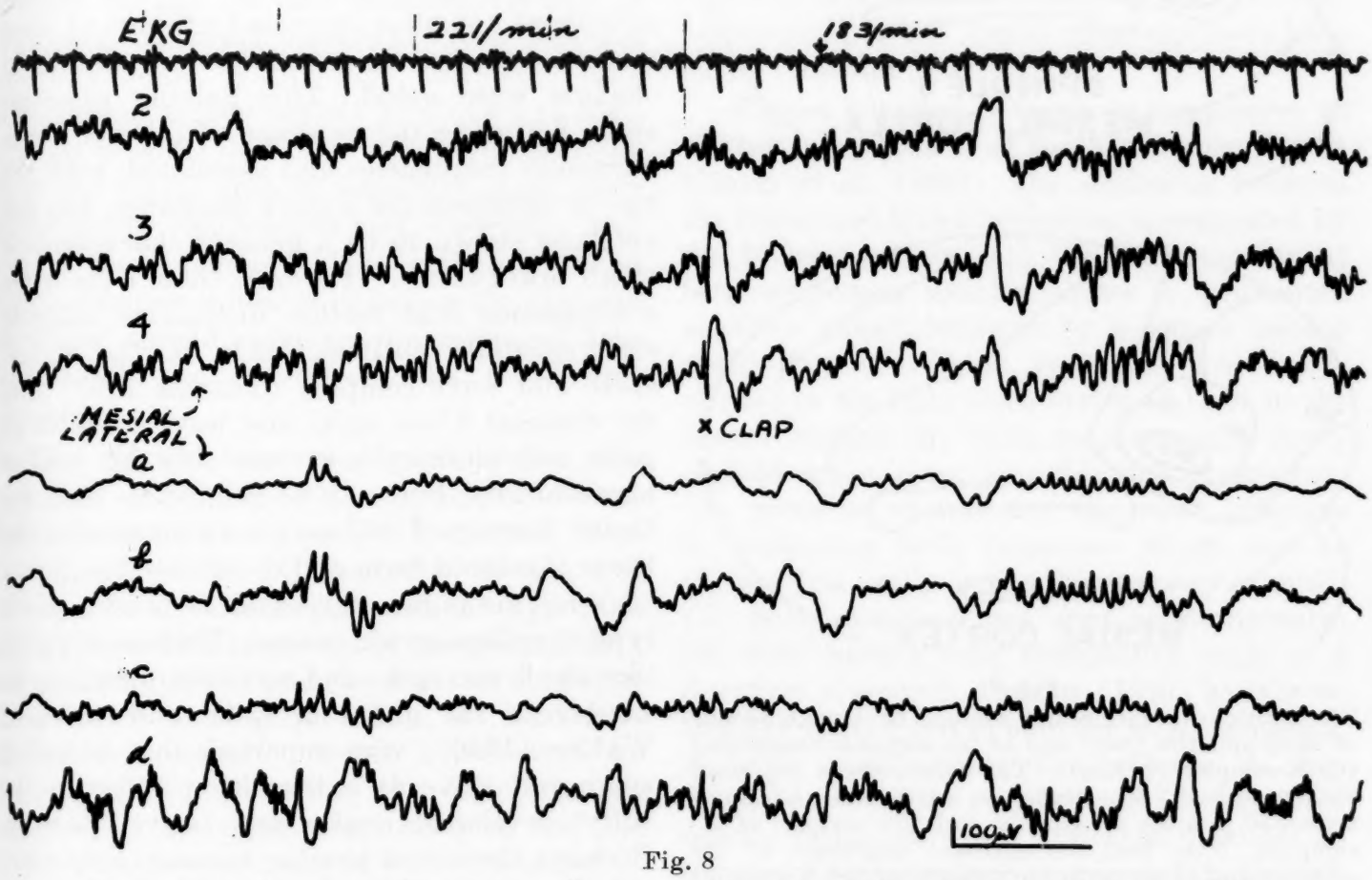


Fig. 8

Response similar to the K-complex. Channel 1 shows the EKG. Channels 2-4 show activity from the anterior limbic area of the mesial surface (Mary); channels 5-8 show activity from suprasylvian gyrus (a, b) and lateral gyrus (c, d) of the lateral surface. Note the diphasic slow wave complex, following the sharp wave, that appears on the mesial surface as the electrographic response to a hand-clap during a light sleep state of the cat. Following this response which resembles the K-complex in man, a slight transient slowing of the heart rate is seen. Note also the sleep spindles.

Fig. 7

Areas of the mesial cortex showing best photic driving at different frequencies of stimulation. The encircled values represent the range of the amplitude (in microvolts) of photic responses averaged from at least 150 selections of good driving from 28 electrodes in 4 different cats. The position of the higher value in the range indicates the approximate locus of the largest amplitude of photic response within that area. Note that the area showing the largest amplitude of photic driving varies according to the frequency of the stimulus.

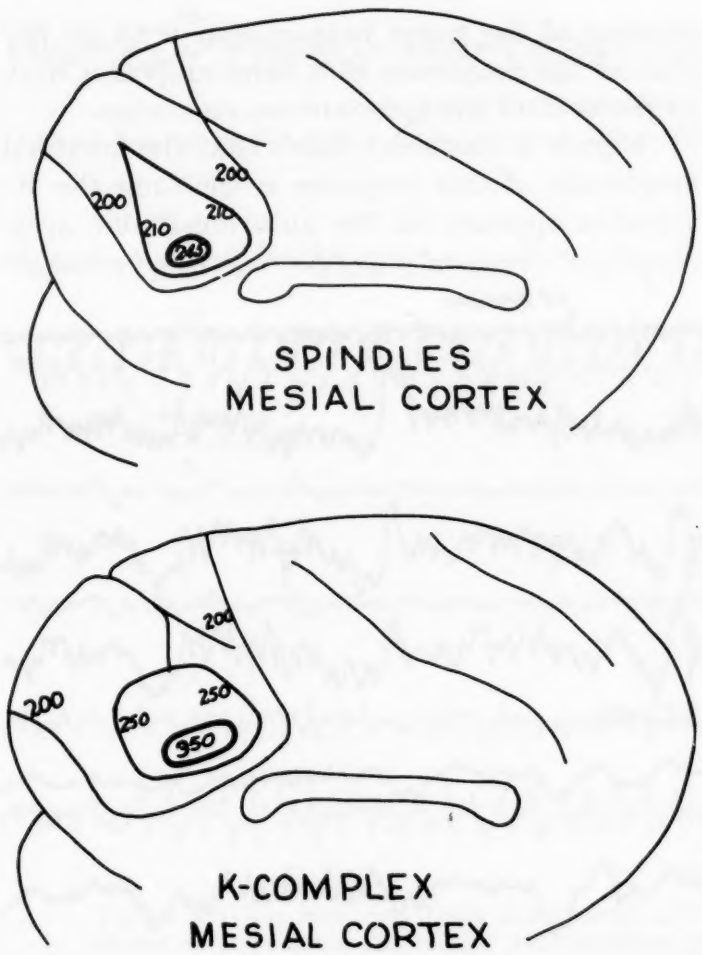


Fig. 9

Distribution on the mesial surface of the amplitude of sleep spindles (top) and of the response resembling the K-complex (bottom). The values shown represent the (peak-peak) amplitude (in microvolts), averaged from 350 samples of spindles and 200 samples of K-complex. Note that the maximal amplitude of the spindles and of the response resembling the K-complex is seen on the anterior limbic area, and also that the distribution of amplitude is similar for these 2 electrographic phenomena.

addition, the amplitude distribution is similar for spindle bursts and for the response resembling the K-complex. The frequency of these spindles is more often 12/sec. than 11/sec. and, at times, is as low as 10/sec. and as high as 15/sec.

DISCUSSION

The frequency of seizure discharges has received little attention in the past and has not been significantly correlated with any particular variable. Figure 1 shows a typical epileptogenic after-discharge of 16-18/sec. from the anterior limbic area. Recording from similar regions, Kaada (1951) reported frequencies up to 18/sec., but listed the lower limit as low as 12/sec. In figures 2 and 3 the halving of the 18/sec. seizure activity to the slower 9/sec. activity, noted after numerous stimulations eliciting many seizure discharges, was associated with a rise in threshold of seizure discharge. Delgado (1958) reported that after long-termed stimulation of subcortical structures a similar increased amount of slow seizure activity was seen, but no threshold changes were noted. This halving phenomenon, featuring the presence of (slower) subharmonic frequencies and associated with the rise in threshold for seizure discharge, has not yet been shown to be a general characteristic of all brain tissue. However, these data offer a suggestion that certain distinctive, clinical electrographic entities, such as the 6/sec. spike and wave complex (Thomas 1957) and the classical 3/sec. spike and wave complex of petit mal epilepsy may not only be related harmonically, but may be related so that the faster frequency (6/sec.) may represent the lower threshold form and the slower frequency (3/sec.) the higher threshold form of a given type of epileptogenic process. Thomas suggests that the 6/sec. spike and wave complex may be similar to the phantom spike and wave of Walter (1950), who reported this phantom spike and wave as a transition stage to the fully developed spike and wave pattern. Perhaps there is a similar harmonic relationship between 14/sec. and 6 (to 7)/sec. positive spikes of ''thalamic and hypothalamic'' epilepsy (Gibbs 1952). Gibbs (1952) has stated that in the young, adolescent age group, when this type of electrographic abnormality is seen most frequently, the 14/sec. spikes are seen more often than the slower form. It seems possible that the 14/sec. spikes may represent the lower threshold form and the 6 (to 7)/sec. spikes the higher threshold form, seen more often in older age groups, after many 14/sec. spikes have occurred in the earlier years.

Figure 4 shows high amplitude spike and wave complexes, representative of the full-blown seizure of the limbic area. Kaada (1951) observed this same type of seizure discharge in two cats. Also, Tükel and Jasper (1952) showed that the spike and wave complex, similar to that seen in petit mal epilepsy, is com-

monly seen in the parasagittal disorders of man.

The limbic seizure activity seen in figure 4 spreads to the hippocampus, which is assumed to be involved in many of the temporal lobe seizures of man. Clinically, the limbic seizures in the cat are psychomotor-like in character, featuring bizarre behavior patterns and autonomic dysfunction. Although data from the cat cannot readily be applied to man, it seems possible that some seizures originating from the limbic area of man may show many psychomotor components and, therefore, may appear as a temporal lobe epilepsy. These limbic seizures would only indirectly, through electrical spread, involve the temporal lobe and its deeper structures, like the hippocampus.

The clinical seizures of the limbic area typically terminate with voracious eating. Similar responses have been reported from stimulation of the hippocampus (Coons and Miller 1958), various parts of the hypothalamus (Hess 1958), especially the mammillary body (Maire 1956) and the anterior thalamus (Maire 1956 and Smith 1958). At least part of the "emotional" circuit popularized by Papez (1950), including the hippocampus, mammillary body, anterior thalamus and the limbic area, seems involved in the response of voracious eating.

Figure 7 demonstrates the importance of the frequency of the photic stimulus in determining the area of maximal response. Similarly, the frequency of the electrical stimulus, applied directly to the brain, is important in determining the nature of the movement elicited. (See previous paper in this journal.) The factor of frequency, therefore, seems important in determining the response of the brain to both internally and externally applied stimuli.

Although the maximal photic response of the mesial area is found, as expected, on the posterior mesial surface, clear photic driving is seen, at times, from the anterior mesial surface. The anterior limbic area, for example, shows photic driving and is far anterior to the "classical visual cortex". Although these visual responses may well be the result of spread through a volume conductor, other nonvisual activity within the anterior limbic area may be significantly influenced by this electrical spread. Visual responses from the anterior limbic region may also result from neuronal transmission from the anterior thalamic nuclei, where visual responses have been noted (Gastaut 1958).

Figure 8 shows a response suggestive of the feline equivalent of the K-complex of man (Davis *et al.* 1939). The similarity between the feline and human response is suggested by the following facts: (1) the configuration of both responses usually shows a prominent negative phase, followed by a longer lasting positivity; (2) these responses are easily elicited in the light sleep states and not in the deeper states; (3) both responses are easily elicited when sleep spindles are prominent; (4) acoustic stimuli are the most effective in producing both responses which can be elicited less easily with other sensory stimuli; (5) both responses are seen spontaneously; (6) both have a long excitability cycle of a duration of seconds. Brazier (1949) has shown that the EEG focus in man for slow transients, probably spontaneous K-complexes, is far-frontal and midline; Gastaut (1954) has noted similar responses which appeared maximal on the cingular gyrus both in man and in the cat. Figure 9 shows that on the mesial surface of the cat the more precise locus of the maximal K-complex is in the anterior limbic area, just anterior and dorsal to the anterior limit of the corpus callosum. Figure 9 shows a similar locus for the maximal amplitude of the spindles. Although showing only topographical similarity, this figure would suggest a close relationship between the K-complex and the sleep spindles. Furthermore, the K-complex usually appears maximal during the spindle state. It would also seem likely that the nucleus projecting to the anterior limbic region, the anterior medial thalamic nucleus, may in some way be involved in the production of spindles and the K-complex, although the nonspecific thalamic nuclei appear maximally involved in the production of spindles (Ralston and Ajmone-Marsan 1956).

SUMMARY

1. These studies feature recording from the supracallosal mesial cortex of the conscious, unanesthetized cat.

2. Frequencies of 16-18/sec. are commonly seen in the short-termed seizure discharges from intensive electrical stimulation of the anterior limbic area.

3. After numerous stimulations eliciting considerable epileptogenic activity, seizure discharges from the anterior limbic area show a decrease in the amount of faster 16-18/sec. seizure activity, an increase in the amount of the (slower) subharmonic 8-9/sec. seizure activity and an increase in the threshold to seizure discharge.

4. Full-blown electrographic seizures of the limbic area feature high amplitude 2-3/sec. spike and wavelike complexes, not usually seen on the lateral surface, but spreading to the hippocampus.

5. Full-blown clinical seizures of the limbic area featuring bizarre behavior patterns and autonomic dysfunction are psychomotor-like in character.

6. Photic driving of relatively high amplitude is seen well on the posterior mesial surface, especially at the frequency of 5/sec. Photic driving can also be seen on the most anterior portion of the mesial surface.

7. The area showing photic driving of the highest amplitude varies according to the frequency of the light flashes.

8. Responses resembling the K-complex of man are seen in the cat.

9. The area on the mesial surface, showing the maximal amplitude of the response resembling the K-complex, is the anterior limbic area where sleep spindles of 12/sec. are also maximally represented.

RÉSUMÉ

1. Cette étude présente les tracés du cortex médian supracalleux du chat éveillé et nonanesthésié.

2. Une fréquence de 16-18/sec. s'observe fréquemment dans les courtes décharges convulsives résultant de la stimulation intense de la région du limbe antérieur par l'électricité.

3. Après de nombreuses excitations causant une activité épileptogène marquée, les décharges convulsives de la région du limbe antérieur manifestent une diminution de l'activité convulsive rapide (16-18/sec.), une augmentation de l'activité convulsive subharmonique lente (8-9/sec.) et une augmentation du seuil de décharge convulsive.

4. Les convulsions venant de la région du limbe, quand elles sont pleinement développées, présentent sur le tracé des complexes de haute amplitude (2-3/sec.) en clocher et ondulés, qui ne sont pas d'ordinaire observés sur la surface latérale, mais qui s'étendent dans la direction de l'hippocampe.

5. Les caractères cliniques des convulsions venant de la région du limbe, y compris des troubles bizarres du comportement et du système autonomique, suggèrent une nature psychomotrice.

6. Un entraînement des activités occipitales d'amplitude relativement élevée s'observe à la surface médiane postérieure spécialement à la fréquence de 5/sec. Un effet similaire s'observe à la partie antérieure de la surface médiane.

7. Les régions dont l'entraînement a l'amplitude la plus élevée varient avec la fréquence des éclairs lumineux.

8. Des réponses ressemblant au complex-K de l'homme s'observent chez le chat.

9. La région de la surface médiane où la réponse analogue au complex-K a l'amplitude la plus élevée est la région du limbe antérieur où l'on observe aussi le maximum de « spindles » de sommeil de 12/sec.

ZUSAMMENFASSUNG

1. In dieser Arbeit wird über Ableitungen der supra-callösen medialen Hirnrinde an einer wachen, nicht anaesthesierten Katze berichtet.

2. Bei intensiver elektrischer Reizung des anterioren ''limbischen'' Bereiches werden im allgemeinen Frequenzen von 16-18 Hz in den kurzfristigen Anfallentladungen beobachtet.

3. Nach zahlreichen Reizungen, die eine beachtliche epileptogene Aktivität hervorrie-

fen, zeigen die Anfallentladungen des anterioren ''limbischen'' Bereiches eine Abnahme der schnelleren 16-18 Hz und eine Zunahme der (langsameren) subharmonischen 8-9 Hz Wellen; der Schwellenwert der Anfallentladungen erhöht sich.

3. Ausgeprägte elektroencephalographische Anfälle des ''limbischen'' Bereiches zeigen "spike and wave'' — ähnliche Komplexe von hoher Amplitude und 2-3 Hz Frequenz; gewöhnlich werden diese Komplexe nicht an der lateralen Hirnoberfläche beobachtet, sondern zeigen eine Ausbreitung zum Hippocampus hin.

5. Ausgeprägte ''klinische'' Anfälle des "limbischen''-Bereiches zeigen Züge bizarren Benehmens, einer autonomen Dysfunktion und sind somit psychomotorischen Anfällen ähnlich.

6. ''Photic driving'' von relativ hoher Amplitude ist an der posterioren medialen Hirnoberfläche, besonders bei einer Frequenz von 5 Hz, gut zu beobachten. ''Photic driving'' wird ebenfalls am vordersten Teil der medialen Hirnoberfläche gesehen.

7. Der Bereich, welcher ''photic driving'' höchster Amplitude aufweist, ändert sich mit der Frequenz der Lichtblitze.

8. Reaktionen, die dem K-Komplex des Menschen entsprechen, werden auch an der Katze gefunden.

9. Der Bereich der medialen Hirnrinde mit maximaler Amplitude der K-Komplex ähnlichen Reaktionen ist der anteriore ''limbische''-Bereich, who auch Schlafspindeln von 12 Hz am häufigsten auftreten.

REFERENCES

BRAZIER, M. A. B. Electrical fields during sleep. *EEG Clin. Neurophysiol.*, **1949**, *1*: 195-204.

COONS, E. E. and MILLER, N. Personal communication, **1958**.

DAVIS, H. Electrical reactions of the human brain to auditory stimuli during sleep. *J. Neurophysiol.*, **1939**, *2*: 500-514.

DELDAGO, J. M. R., USHIYAMA, J. and GAROTTE, L. Effects of repeated cerebral stimulation in monkeys. *Fed. Proc.*, **1958**, *17*: 34.

GASTAUT, H. in *Brain Mechanisms and Consciousness*, Chas. C. Thomas, Springfield, **1954**.

GASTAUT, H. Personal communications, **1958**.

GIBBS, F. A. and GIBBS, E. L. *Atlas of Electroencephalography*, Vol. II, Addison-Wesley Press, Cambridge, Mass. **1952**.

HESS, W. R. in HUGHES, J. R. Functional Organization of the Diencephalon-Translation of Hess' *Das Zwischenhirn*. Grune and Stratton Inc., New York, **1958**.

KAADA, B. R. Somato-motor, autonomic and electrocorticographic responses to electrical stimulation of ''rhinencephalic'' and other structures in primates, cat and dog. *Acta physiol. scand.*, **1951**, *24* (Suppl. 83): 1-285.

MAIRE, F. W. Eating and drinking responses elicited by diencephalic stimulation in unanesthetized rats. *Fed. Proc.*, **1956**, *15*: 124.

PAPEZ, J. W. A proposed mechanism of emotion. *Arch. Neurol. Psychiat.*, Chicago, **1937**, *38*: 725-743.

RALSTON, B. and AJMONE-MARSAN, C. Thalamic control of certain normal and abnormal cortical rhythms. *EEG Clin. Neurophysiol.*, **1956**, *8*: 559-582.

ROSE, J. E. and WOOLSEY, C. N. Structure and relations of limbic cortex and anterior thalamic nuclei in rabbit and cat. *J. Comp. Neurol.*, **1948**, *89*: 279-340.

SMITH, O. A. Personal communication, **1958**.

THOMAS, J. A rare electroencephalographic pattern: the six per second spike and wave discharge. *Neurol.*, **1957**, *7*: 438-442.

TÜKEL, K. and JASPER, H. The electroencephalogram in parasagittal lesion. *EEG Clin. Neurophysiol.*, **1952**, *4*: 481-494.

WALTER, W. GREY, in HILL, J. D. N. and PARR, G. *Electroencephalography*, MacMillan, New York, **1950**.

Reference: HUGHES, J. R. Studies on the supracallosal mesial cortex of unanesthetized, conscious mammals. I. Cat. Electrical activity. *EEG Clin. Neurophysiol.*, **1959** *11*: 459-469.

NEW SUPPLEMENT

OBNUBILATIONS, COMAS ET STUPEURS

Études électroencéphalographiques

by

H. FISCHGOLD
Electroencephalographer of the Hôpital de la pitié

and

P. MATHIS
Research Associate at the Institut National d'Hygiène

SUPPLEMENT N° 11

ELECTROENCEPHALOGRAPHY AND CLINICAL NEUROPHYSIOLOGY

An International Journal

A volume of 126 pages, with 54 figures (7½ x 11 inches) 3,000 French frs.

For nearly 15 years, at the Sainte-Anne Hospital first, then at the Pitié Hospital, the authors studied the comatose states with electroencephalographic and neuro-vegetative polygraphic techniques. Most of the patients investigated were affected by neuro-surgical conditions and the post-traumatic comas constituted the largest group among them.

In the beginning, the authors investigated mainly the relatively acute forms of coma, resulting from hypersomnia associated with more or less extensive brain lesions and with neuro-vegetative disturbances. On the basis of these studies, the coma can be classified into three stages: I, II and III, characterized by their increasing depth, by progressive loss of contact with the environment, by an increased difficulty of arousal and by a loss of the principal cephalic reflexes (palpebral, corneal and swallowing).

There exists no specific EEG pattern or rhythm characteristic for comatose states, for even if a tendency to slow activity is an undisputable fact, the EEG tracings of comatose patients often show alpha or theta frequencies which predominate in the parieto-occipital regions whereas the slow wave forms originate from more anterior head regions. On the other hand, according to the authors, the criteria, which can be taken as the measure of the severity of the comatose state, are the reactivity of the tracing to external stimuli, its periodicity or monotony, as well as the cortico-vegetative correlations investigated by the simultaneous recording of the EEG and of the respiratory cycle.

Resuscitation procedures, artificial respiration and the prolonged survival of comatose patients makes it possible to observe novel aspects of the evolution of comatose states; hypersomnia disappears and the vegetative disturbances regress but major psycho-motor deficits persist. Newly found post-comatose syndromes (hypertonic stupor, psycho-motor dissolution) are now under study.

The problem of acute cardio-respiratory failures and that of the "death of the brain" are studied with the EEG and make it possible to visualize the possibility of an electrographic study of the collapse and of the acute disturbances of cerebral circulation.

This volume will be of service, firstly to the electroencephalographers who study severe head injuries which are becoming more and more numerous; however, without going into too many technical details, the authors have succeeded in writing a study which will be useful for neurologists, neurosurgeons, and for all those interested in the problems of forensic medicine and resuscitation techniques.

I. Patient material. — II. Methods of examination; Neurological examination. Diagnostic laboratory procedures. — III. Electroencephalographic symptomatology of comatose states. — IV. States of coma: State I: Clouding of consciousness. State II: Coma in the strict sense. State III: Deep coma. State IV: Acute cardio-respiratory failure. Death of the brain. Discussion V. — Evolution of comatose states: Acute evolution (States I, II, III). Chronic evolution: Prolonged clouding of consciousness. Post-comatose hypertonic stupor (case histories 1 and 2). Mutism: Psychomotor regression in the infant. Discussion. — Bibliography.

Order for immediate delivery from

Masson et Cie, Publishers
120 Blvd. St. Germain, Paris VI-e
(Price 3,000 fr.)

or

THE EEG JOURNAL
3801 University Street, Montreal
(Price $8.00)

CONDITIONING OF RETICULAR FORMATION STIMULATION EFFECTS [1]

J. P. SEGUNDO, M.D., J. A. ROIG, B.A. and J. A. SOMMER-SMITH, B.A.
Departamento de Electrobiología, Instituto de Investigación de Ciencias Biológicas, Montevideo, Uruguay

(Received for publication: September 12, 1958)

Environmental stimuli are paramount among issues that participate in determining the transition from sleep to wakefulness or the passage from a wakeful but inattentive condition to one of alert vigilance, attack or defence. It is generally conceded that their influence is exerted through activation of central brain stem structures, direct excitation of which induces comparable types of performance (Hess 1956; Moruzzi and Magoun 1949; Rossi and Zanchetti 1957; Segundo 1956). The purpose of the present series was to explore the possibility that systematic association of a tone with direct stimulation of such nuclei might modify the response of the animal to the sound. As will be seen, this is indeed the case: after repeated reinforcement, a previously indifferent tone will eventually be capable, per se, of provoking a behavioral response analogous to that produced by the reticular stimulation and also of awakening the sleeping animal.

MATERIAL AND METHODS

Experiments were made on 7 adults cats carrying electrodes implanted chronically according to a technique described elsewhere (Segundo, Arana and French 1955). Cortical records (sensori-motor and auditory) were obtained through extradurally placed pairs of enameled stainless steel wires (.125 mm. in diameter; bared a length of 1-3 mm.). Deep stimulation and/or recording (centre median of thalamus-CM, mesencephalic reticular formation-MRF, hippocampus) was obtained with electrodes consisting in a pair of stainless steel wires (.125 mm. in diameter insulated except at the tips and fastened to a thicker wire strut, reaching to within 10 mm. of the tips).

Observations were carried out in a quiet environment where behavior could be observed (without the animal seeing the investigator) and EEG recorded on a 6-channel Grass III-D machine. Absolute (unconditioned or original) stimuli consisted in electrical excitation (waveform, sinusoidal; frequency, 50-150 c/sec.; duration 4 or 10 sec.) applied through deep electrodes to CM (4 cats) or MRF (3 cats). Voltages (see below) were adjusted as to produce, on each application, a stereotyped response. Animals, site of stimulation and responses are given in table I. A tone (generated by a Hewlett Packard 200 AB audio-oscillator and a loudspeaker) was used as indifferent (and eventually conditioned) stimulus in 6 cats; frequency and duration varied from one animal to another (200, 700, 1000,

TABLE I

Preparation serial number	Absolute stimulus to	Conditioned stimulus (tone)	Response
9	MRF	200 c/sec. 10 sec.	Head turning
10	CM	1000 c/sec. 4 sec.	Head turning
11	CM	1000 c/sec. Cessation	Cowering
13	MRF	700 c/sec. 4 sec.	Cowering
14	MRF	3000 c/sec. 4 sec.	Head turning
15	CM	1600 c/sec. 4 sec.	Rolling
16	CM	1600 c/sec. 4 sec.	Cowering

[1] Supported by grants from the Rockefeller Foundation and Donación Arana.

1600 or 3000 c/sec.; 4 or 10 sec.) but were constant for each preparation; intensity was the same for all acoustic stimuli used.

Animals were followed through three stages. Stage I: the tone was applied alone a large number (hundreds) of times until no behavioral or electroencephalographic response occurred. Stage II: the tone was systematically associated to the absolute stimulus (both having identical duration, the second half of the tone coincided with the first half of the excitation). Sessions were carried out daily (at different times of the day), lasted approximately one hour and involved up to 25 reinforcements at 2-5 min. intervals. The effect of the tone applied alone was tested in each session. After establishment of a consistent acquired response to the tone (see Results), an effort was made to obtain classical types of inhibition: external (with unexpected stimuli) and internal discriminatory, conditioned, delay and extinction (by non-reinforcement of tones of different frequencies, of tones preceded by a buzzer, etc.). Stage III: lesions were placed through the implanted electrodes (in CM, 2 cases; in MRF, 3 cases) with the purpose of determining whether destruction at the site stimulated (or elsewhere) modified the learned response.[1] This entire procedure took place during wakefulness.

The awakening potentialities of the auditory stimulus per se were explored during natural sleep: (1) at the beginning of the entire procedure (the very first tone or one of the first dozen at the most was applied under conditions of sleep); (2) at various points of stage I (during and after habituation); (3) at various points of stage II (during reinforcement, discrimination, extinction, etc.); (4) at stage III (after lesion). An animal was considered asleep when the characteristic attitude (lying on its belly or side, eyes closed, relative immobility and non responsiveness) was associated with a large amplitude, slow EEG. Such a situation was occasionally difficult to encounter for behavior might be typical for minutes or hours and the EEG remain one of wakefulness or, at the most, relaxation (Rowland 1957; Segundo, Arana and French 1955; Sharpless and Jasper 1956). Two procedures were followed in such cases (*a*) waiting until the animal finally did sleep (in the early a.m. perhaps) (Segundo, Arana and French 1955; Sharpless and Jasper 1956); (*b*) leaving it overnight in a dish with water (which forced it to remain erect) and testing the following day or evening (Rowland 1957).

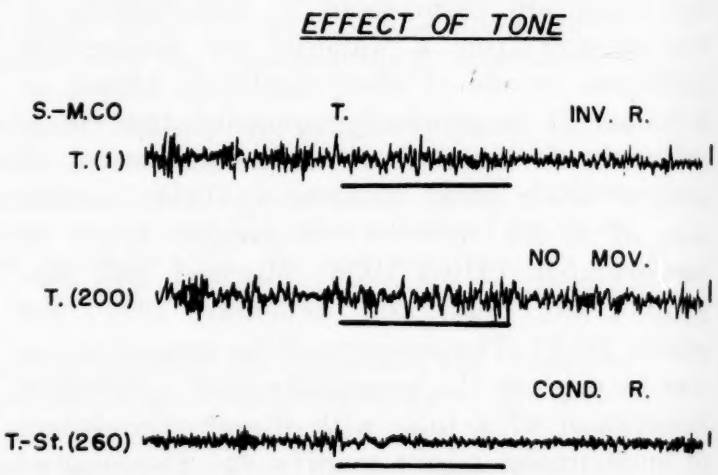


Fig. 1

Effect of tone alone upon wakeful animal (records from right sensori-motor cortex). T (1); first presentation produces EEG "desynchronization" and an investigation reflex. T (200): after 200 applications, no behavioral or EEG effect. T-St (260): after 260 reinforcements, the tone alone produces a conditioned response, an evoked potential and an EEG "desynchronization". COND. R., conditioned response; INV. R., investigation reflex; NO. MOV., no movement; S-M. CO., sensori-motor cortex; T., tone; T.-St, tone usually reinforced by absolute stimulation. Calibration for all figures, 1 sec., 50 μV.

Instances of awakening or alerting produced by the cessation of a stimulus are current in human experience. Accordingly, the seventh cat was submitted to a continuous tone of 1000 c/sec., periodic interruptions of which were followed (2 sec. later) by an absolute electric stimulus (of 2 sec. duration) to CM. The purpose was to modify, if possible, the response provoked by the cessation of the tone.

[1] Lesions were produced electrolitically, under ether anesthesia (without electrolysis). Previously, animals were subjected to a similar anesthesia: no modifications occurred in responsiveness as tested after behavioral recovery.

RESULTS

Results concern variations in response to tone. *Stage I.* (i) Cat awake. The first tones alerted the preparation and produced a typical orienting reflex. With repetition of stimulus, the response attenuated gradually and finally disappeared (habituation). Parallel to reduction of behavioral response (but not coinciding exactly with it) the generalized EEG voltage reduction-frequency increase (''desynchronization'', ''activation'') produced by early tones became less noticeable and was abolished (fig. 1); occasionally, an increase in amplitude of pre-existing slow rhythms was produced by the habituated tone (Buser and Roger 1957; Fessard and Gastaut 1954; Gastaut *et al.* 1957).

(ii) Cat asleep. Presentation of the first tones to the sleeping animal produced, in every case, typical behavioral and EEG arousal (fig. 2). If the stimulus was reapplied on the same night, partial or total attenuation of the effect occurred (Sharpless and Jasper 1956); arousal-habituation came earlier in successive nocturnal sessions in a fashion grossly parallel to that of alerting-habituation in diurnal sessions. EEG aspects of arousal survived longer than behavioral manifestations. Eventually, not even the first tone caused the slumbering animal to respond (fig. 2). This occurred also in cats in which no more than 3 nocturnal sessions (with up to 3 tones in each) were carried out during stage I, which would indicate that repeated

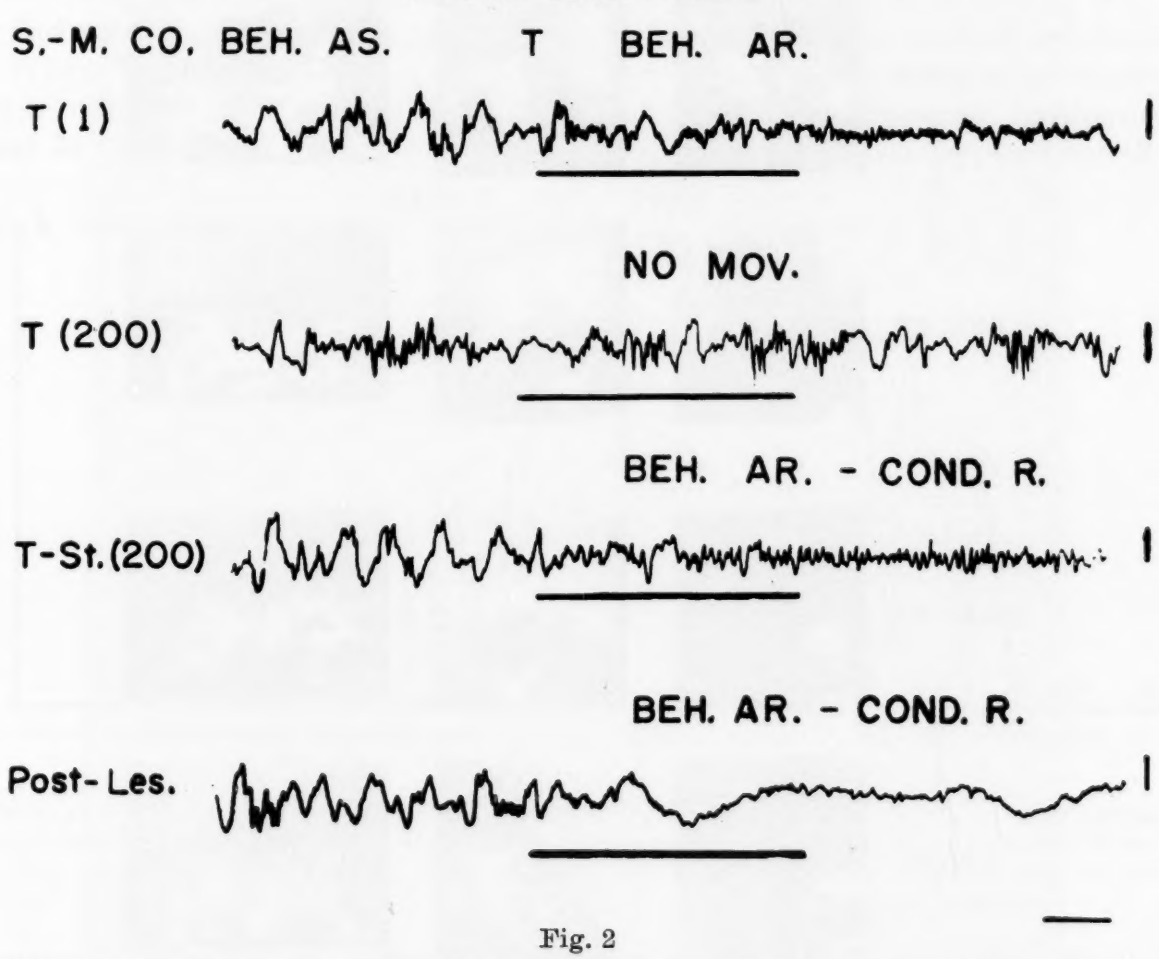


Fig. 2

Effect of tone alone upon sleeping animal (records from right sensori-motor cortex). T (1): first presentation produces EEG and behavioral arousal. T (200): after 200 applications, no behavioral or EEG effect. T-St (200): after 200 reinforcements, the tone alone produces EEG and a behavioral arousal and the conditioned response (head movement). Post-Les.: after electrolytic destruction of area surrounding electrode (MRF) the effect of the tone persists. BEH. AR., behaviorally aroused; BEH. AS., behaviorally asleep; Post-Les., post-lesion.

application during wakefulness suffices to abolish the arousing potentialities of a given stimulus.

Stage II (i) Cat awake. Absolute effects produced by electrical excitation of CM or MRF consisted in: (A) head turning to side contralateral to stimulus, mydriasis, widening of palpebral fissures (3 cats); (B) head turning, mydriasis, widening of palpebral fissures, retraction of body, cowering (as if retreating to the side of the stimulus) and, occasionally, urination and defecation (2 cats); (C) as (B) plus rolling (on to the side of the stimulus) (1 cat) (fig. 3).

The first tones of stage II were followed by no response. After 10-30 associations, the tone alone evoked behaviour that outlined orienting, startle, flinching or cringing responses (if previously involved in "spontaneous" activity, cessation of latter): such ef-

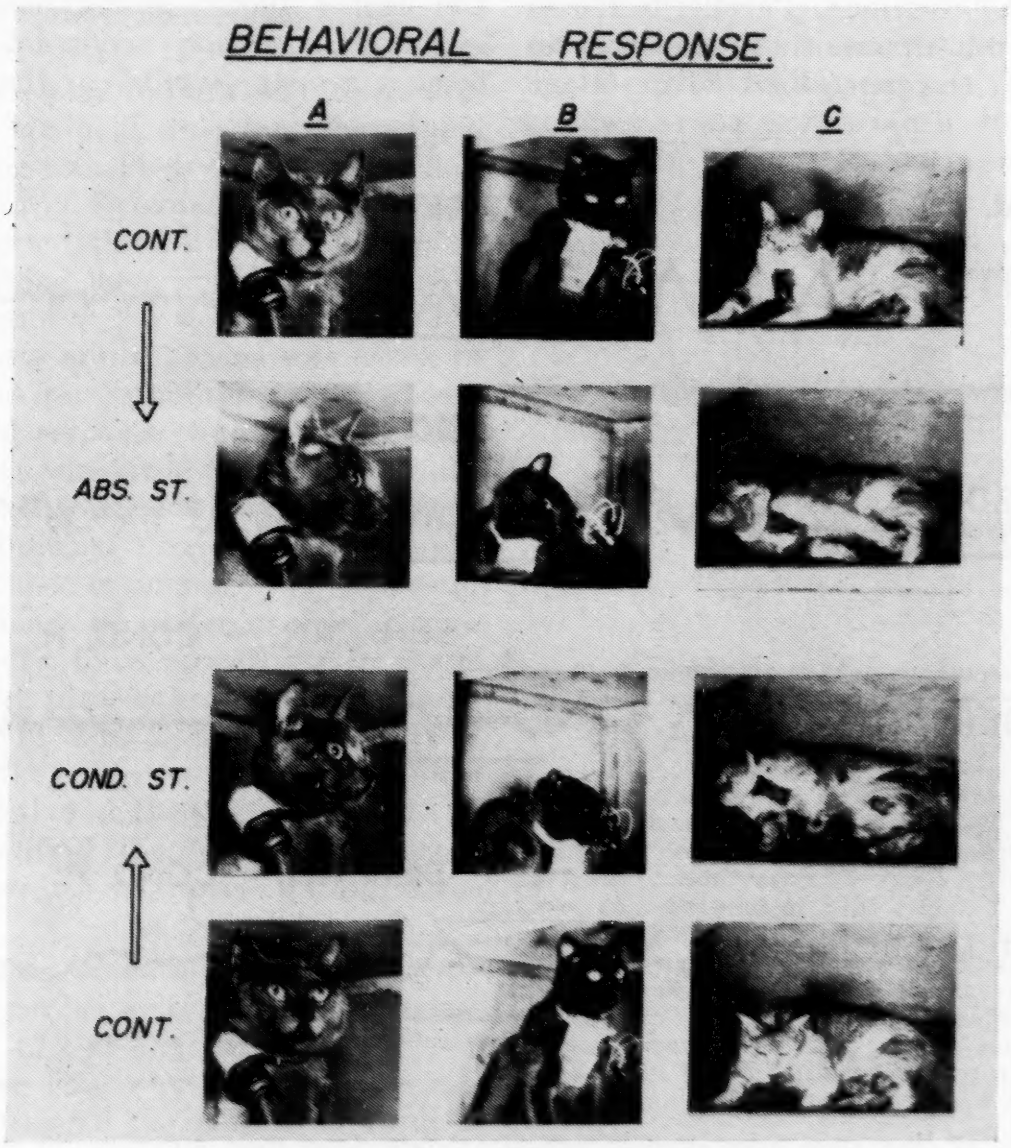


Fig. 3

Absolute and conditioned behavioral response. First line from top, control previous to absolute stimulus. Second line, effect of absolute stimulus (to brain stem). Fourth line, control previous to conditioned stimulus. Third line, effect of conditioned stimulus (tone). Column A, head turning, etc. by right mesencephalic reticular formation excitation. Column B, cowering, etc. by right centre median excitation. Column C, rolling by right centre median excitation. ABS. ST., absolute stimulus; COND. ST., conditioned stimulus, CONT., control.

fects varied from one application to another. After 60-600 associations [1], the tone alone induced a behavioral response that reproduced that to the absolute stimulus (see above) (fig. 3). This effect consisted in: (A) head turning (to the side contralateral to the electrode implantation) and mydriasis (also eye opening if previously closed) (3 cases) (fig. 3, A); (B) head turning, mydriasis, flinching, ear retraction and cowering (2 cases) (fig. 3, B); (C) head turning, mydriasis, ear retraction and rolling on its side (1 case) (fig. 3, C). When the absolute effect involved elimination of urine and feces, placement of the animal in the experimental situation sufficed to provoke urination or defecation. In successive sessions, the percentage of positive responses increased rapidly, (with minor oscillations) reaching and remaining at (or close to) 100 per cent (fig. 4).

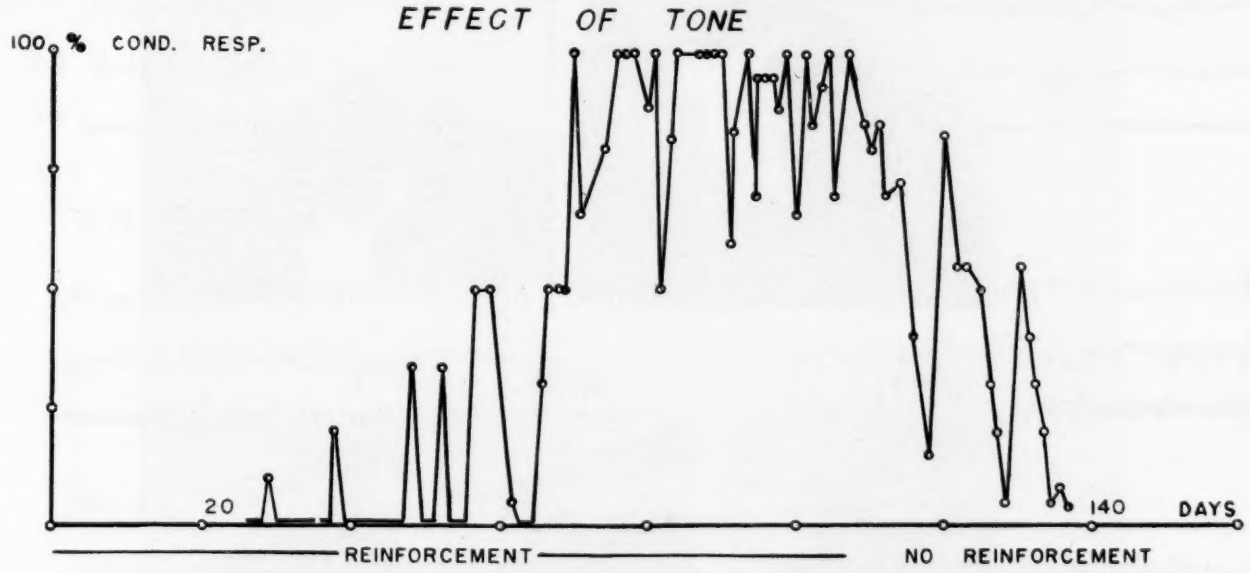


Fig. 4

Curve of ''Learning'' and of ''Extinction'': On abscissae, time in days. On ordinates, percentage of conditioned responses in each daily session. This curve belongs to the first cat in the series: hence (see text), establishment of the conditioned response was a slower process than in preparations that followed. COND. RESP., conditioned response.

Procedures causing inhibition in classical observations avoided or abolished occurrence of the acquired response (Pavlov 1941). If an ''unexpected'' stimulus (knocking, etc.) preceded the tone, the latter failed to produce inactivated (inhibited) tone, the latter would give the typical response (dis-inhibition). When the duration of the first (non-reinforced) portion of the tone was gradually increased, the acquired response first shifted towards the moment of reinforcement and eventually disappeared when a 20-45 sec. ''delay'' had been reached.

In the course of stage II, the EEG response varied also. Soon after reinforcement began, a generalized ''desynchronization'' occurred at the initiation of each tone. This effect was encountered consistently throughout stage II, providing some degree of ''synchrony'' pre-existed; ''activation'' localized the usual effect (external inhibition). After a stage of response to a whole gamut of frequencies (generalization) the animal would react specifically to the re-inforced (e.g., 200 c/sec.) and not to the non-reinforced (e.g., 210, 225, and 250 c/sec.) tones (differential inhibition). If no reinforcement came each time the auditory stimulus followed a buzzer (of 4 sec. duration), the animal would finally not respond to tones preceded by the buzzer (conditioned inhibition) (fig. 5). After repeated application without reinforcement, the response to the positive tone became less frequent and disappeared (extinction). If a foreign stimulus was applied together with an

[1] The number of trials necessary to establish the response decreased from the first (500-600) to the second (200-300) and then to the last group (60-100): this variation may have been due to improvement in the experimental technique.

to one single area was never observed. The initiation of each auditory stimulus also came to produce a clear-cut evoked potential in sensory motor cortex, centre median and mesencephalic reticular formation; very obvious when the animal was relaxed, it became less

conditioned) had been established, repeated application of the inhibitory stimulus led in a few minutes to sleep, both behavioral and EEG (fig. 6).

(ii) *Cat asleep.* After repeated reinforcement, the previously "habituated" tone, be-

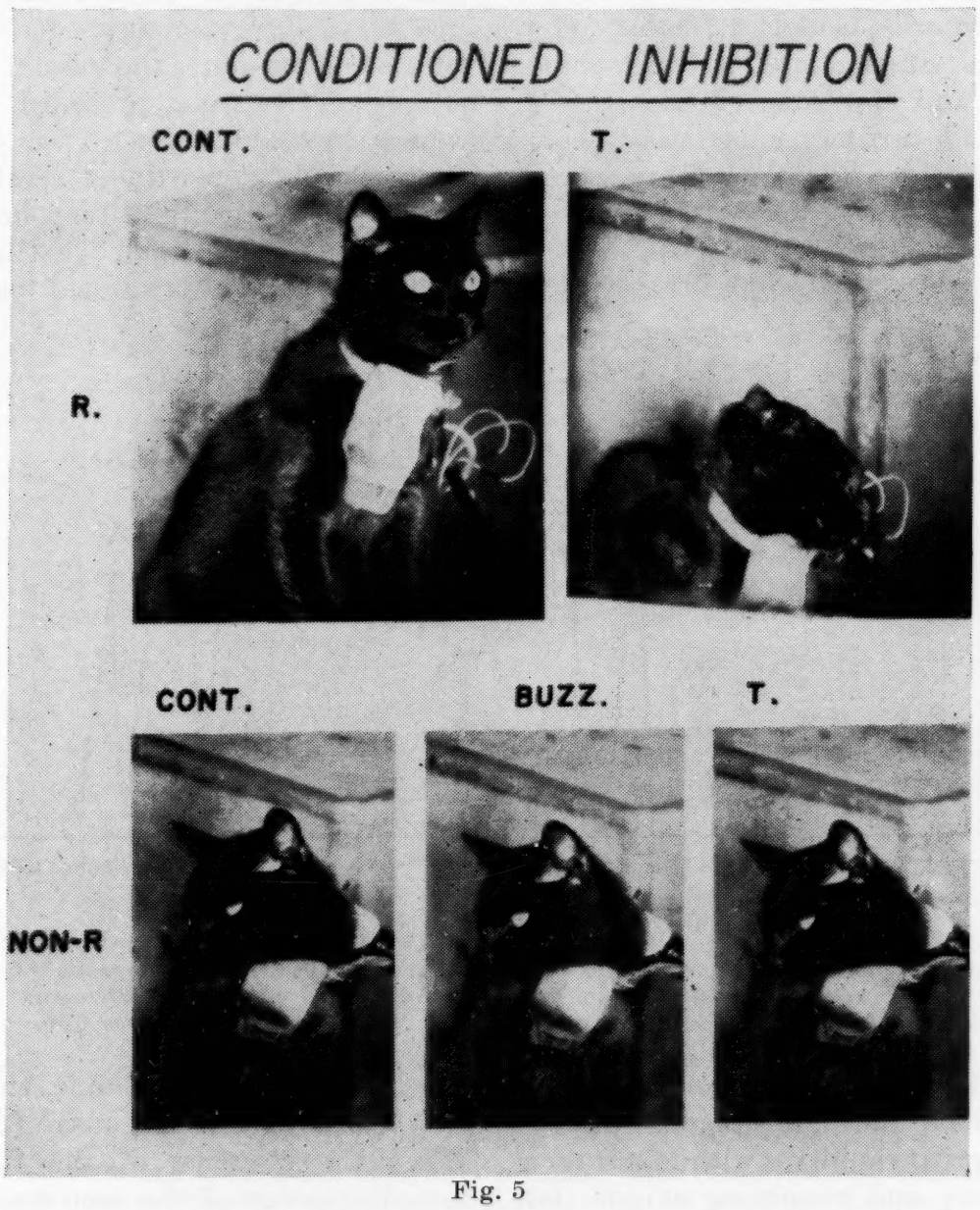


Fig. 5

Conditioned inhibition. Upper line: conditioned cowering response to the usually reinforced tone when applied alone. Lower line: no response to the non-reinforced buzzer-tone association. BUZZ., buzzer: NON-R., non-reinforced; R., reinforced.

noticeable against a background of low voltage-fast activity (fig. 1).

Negative stimuli continued to yield characteristic EEG changes after behavioral effects had disappeared, but finally came to produce no response. When certain situations of non-responsiveness (inhibition of delay or

came again capable of arousing the preparation when applied alone (fig. 2). It is not possible to state how many associations suffice for this to occur but the earliest arousal was produced after 61 reinforcements. At the period when the wakeful animal had learned to react to the tone by a response analogous

to that of the brain stem excitation, arousal from sleep was frequently associated with a similar performance. Tones rendered inoperant in the vigilant cat through extinction, delay or internal inhibition also became incapable of arousing the slumbering preparation. Inhibition through differentiation gave a somewhat more complex picture and figure 7 illustrates the effects when applied during

caused exclusively EEG "arousal" (that was more obvious for the lower frequency) with no associated movements.

In the remaining cat, brain stem excitation came after cessation (CT) of a continuous tone. The beginning of the first presentation caused alerting with EEG "desynchronization" but no change occurred at the termination. After habituation, the tone was inop-

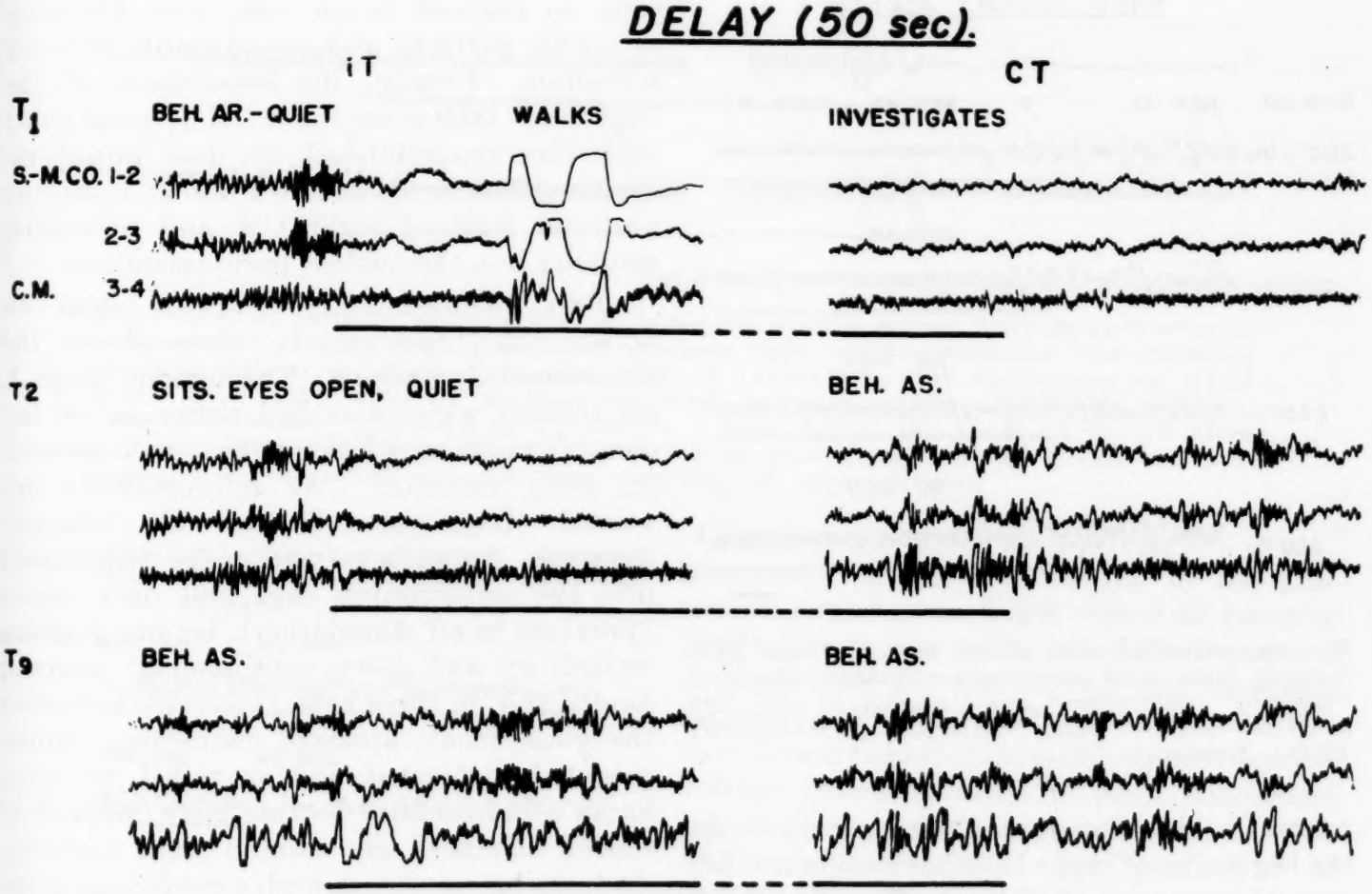


Fig. 6

Hypnogenic effect of "delayed" tone (50 sec. duration) (records from right sensori motor cortex and from centre median). Left column, initiation of tone; right column, cessation of tone. Upper line: on first application (cat awake but quiet) the animal walks and investigates throughout tone. Middle line: on second application (cat awake but quiet), the animal remains quiet and ends behaviorally and electrographically asleep. Lower line: animal behaviorally and electrographically asleep throughout. CM (3-4), right centre median.

sleep of a "positive" tone of 200 c/sec. and of "negative" tones of 210, 225 and 250 c/sec. (to which the awake cat did not reply). The former caused behavioral and EEG arousal associated with a conditioned response. The latter differed: whereas 210 c/sec. aroused behaviorally and electrographically (giving no conditioned response), 225 and 250 c/sec.

erative at both ends. Soon after commencing with reinforcement of CT, alerting and EEG "activation" came to be produced both at iT (initiation of tone) and CT (cessation of tone), the effect of the latter being of longer duration; finally, iT caused little if any behavioral or EEG modifications but CT consistently produced an evoked potential (in

sensory motor area), a generalized EEG "activation" and, behaviorally, cessation of spontaneous activity, immobilization, flinching, startle patterns, blinking, head movements, etc. (fig. 8). A response similar to the absolute effect also appeared after 600 reinforcements but never occurred in more than 50 per cent of the trials. When asleep, the first tones aroused at iT but not at CT;

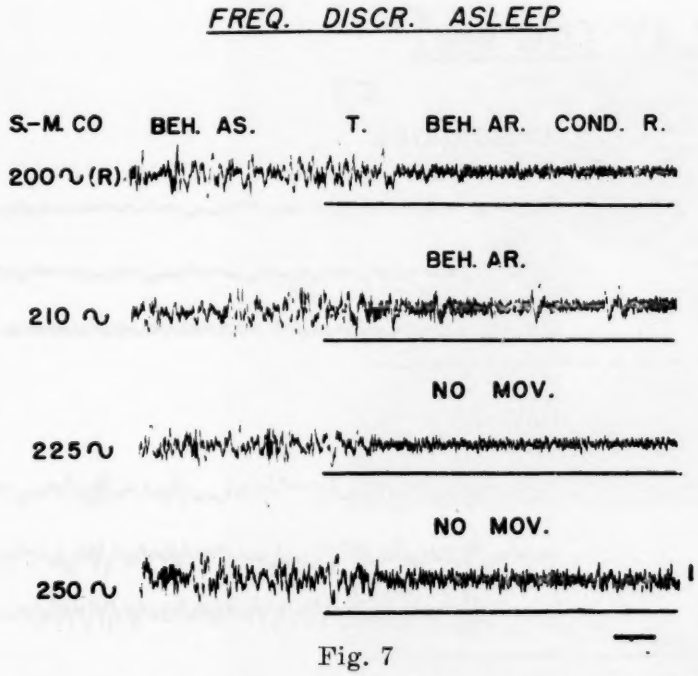


Fig. 7

Frequency discrimination asleep: behavioral and EEG (records from right sensori-motor cortex) effects of "positive" (200 c/sec.) and "negative" (210, 225 and 250 c/sec.) tones. DISCR., discrimination; FREQ., frequency.

arousal habituation ensued during stage I. At the beginning of stage II, behavioral and EEG arousal occurred at iT and CT. Finally iT caused no changes other than a brief EEG "arousal"; CT continued to evoke a complete arousal reaction (fig. 9).

Small (not larger than 1 mm. in diameter) electrolytic lesions were placed terminally in the stimulated locus (CM, MRF) or elsewhere (CM when stimulating MRF or viceversa); no changes were encountered in the "spontaneous" or learned behavior (fig. 2). These observations were supplemented by one animal that, on recovery from a barbiturate anesthesia [1], exhibited a moderate degree of somnolence and on the right side, miosis and paralysis of the nictitating membrane (symptoms disappeared gradually within 30-40 days); a typical response (established previously by reinforcing 100 times a tone of 1600 c/sec. with excitation of rostral C.M.) was abolished and did not reappear after 100 additional trials. The animal was then subjected to classical tone (200 c/sec.) shock to leg technique: after 50 reinforcements, it came to respond to the tone with flinching or startle patterns and, occasionally, with leg retraction. Finally, 100 associations of the first tone (1600 c/sec.) and CM (rostral pole) excitation re-established the lost initial response. Necropsy showed a lesion involving posterior half of right CM and extending medially into the nucleus parafascicularis.

Two complementary features shall be noted: (*a*) *"Spontaneous" behavior in the experimental situation.* Throughout stage I, all animals were quiet and either sat or lay down (exhibiting EEG spindles or, occasionally, sleep patterns). As reinforcement advanced (first part of stage II) behavior changed. Animals refused to be introduced into the conditioning cage and once inside (previous to all stimulation), became restless, walked up and down continuously, meowed loudly and, in three cases, excitedly scratched the glass front, attacked connecting cables, urinated, defecated and/or rolled on their backs (this conduct became more marked as session advanced and stimuli were applied). As training continued, such a performance became less noticeable and disappeared. During the remainder of the study, attitude was one of quiet but vigilant wakefulness with a completely "activated" EEG; spindling was infrequent and throughout a total of nearly 1000 sessions sleep was never encountered [2].

(*b*) *Voltages necessary to reproduce a constant response to brain stem excitation.* At the beginning, 5-7 V. would suffice but, in each animal, these values increased in two ways: (i) "Acute" increase: during each experimental session, successive augmentations of up to a total of 30 per cent became

[1] Nembutal Abbott (35 mg/kg. body weight) with the purpose of repairing sub-cutaneous cables.

[2] Except when induced by repeated applications of "negative" signals (see above).

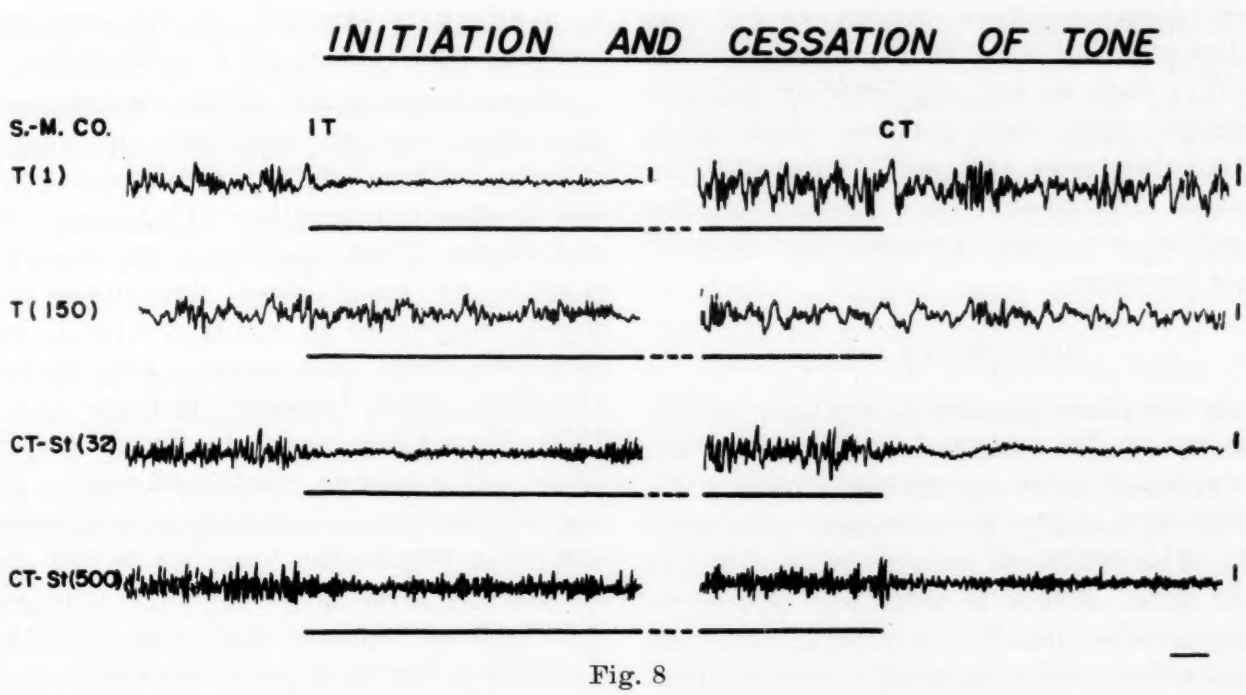


Fig. 8

EEG effects of initiation and cessation of tone upon wakeful animal (records from sensori-motor cortex). T (1): first presentation produces EEG "desynchronization" at initiation (iT) and little or no effect at cessation (CT). T (150): after 150 applications, no effect occurs. CT-St (32): after CT has been reinforced (by centre median stimulation) 32 times, "desynchronization" is caused by CT and, to a lesser extent, iT. CT-St (500): iT gives a slight "desynchronizing" effect; CT provokes an evoked potential and a clear-cut, prolongued "desynchronization". CT, tone cessation; iT, tone initiation.

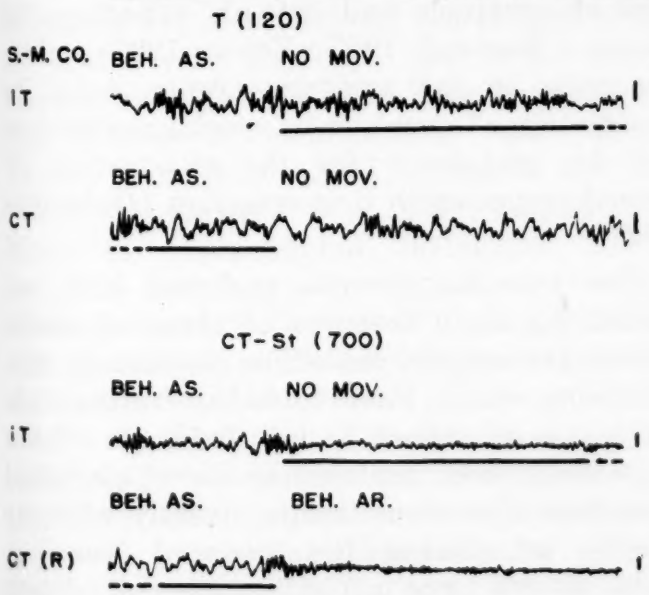


Fig. 9

Effect of initiation and cessation of tone upon sleeping animal (records from sensori-motor cortex). T (120): after 120 applications, no behavioral or EEG effect takes place at tone initiation (iT) or cessation (CT). CT-St (700) after 700 reinforcements of CT, IT produces a short liver EEG "arousal" with no behavioral effect; CT produces EEG and behavioral arousal.

necessary. Intermittent testing in the post-session period showed that threshold returned gradually to normality in 5-24 hours. If voltages were not augmented, the behavioral response attenuated and was abolished. Precise measurement of impedance, current and voltage values involved in each stimulation constitutes a delicate physical problem: preliminary observations were performed in which voltage and intensity were monitored with cathode-ray-oscilloscope and camera. No changes were observed in the electrical characteristics of the stimulus in the course of response attenuation; hence, the latter could be due to a peculiar excitability cycle in the susceptible substratum. Further confirmation is desirable.

(ii) "Chronic" increase. In the course of weeks, threshold went gradually up to about 5 times the initial value (e.g., from 1.5 to 7.5 V., after 5 months and 1500 excitations); resistence (measured on a Heathkit MMI Multimeter) increased in a grossly parallel fashion. Electrodes placed chronically (but not used

for stimulation) produce damage to nervous cells, encapsulation, etc. (Collias and Manuelidis 1957); data as yet unpublished indicate that changes even more intense occur when implanted electrodes are used for excitation. Anatomical alterations plus other changes (polarization, etc.) may provoke this chronic threshold increase.

DISCUSSION

Faced with environmental change, an animal either remains indifferent or exhibits behavior (arousal, alerting, startle, defense, attack) leading usually to increased awareness or safety. The readiness with which a stimulus produces these effects is obviously related to its characteristic quality, intensity, duration and localization (e.g., painful, strong or prolongued excitations are more effective than painless, weak or brief ones). Everyday experience shows, however, that waking or alerting potency varies also with "personal historical" issues such as the number of times the subject has been exposed to the stimulus, the circumstances of its presentation or the connotations it may carry (novel, unexpected or significant excitations are more effective than uniform, anticipated or trivial ones).

Animal experimentation supports the contention that learned mechanisms influence the promotion of basic behavioral shifts and may either decrease or increase the "intrinsic" tendency of a given situation. Repetition of a stimulus (which was effective when novel) leads to abolition of the behavioral (arousal, alerting, startle) and electroencephalographic ("activation", evoked potential) changes induced initially (Jouvet and Hernández Peón 1957; Pavlov 1941; Prosser and Hunter 1936; Sharpless and Jasper 1956). If the indifferent stimulus (e.g., tone) becomes the signal for a painful shock, alerting and startle patterns are again produced (the classical conditioned response will be the final result of the procedure) (Pavlov 1941); the newly attained ability goes together with an acquired capacity for awakening the sleeping animal (Rowland 1957). The present experiments confirm the loss (through repetition) and the re-acquisition (through reinforcement with adequate stimuli) of the arousing and alerting possibilities of a given tone.

Consideration of these reports suggests also that, though constant in their basic aspects, patterns differ in minor details from one instance to another. Orienting, defense and flight effects produced by electrical excitation of brain stem structures resemble closely responses to natural stimuli but, for each electrode placement, are stereotyped (Delgado 1952; Delgado, Roberts and Miller 1954; Hess 1956; Segundo, Arana and French 1955). If a tone is reinforced with a stimulation of this type, a learning process takes place and, as a result, the tone per sé will provoke a response that is identical to the absolute effect (head turning, cowering, rolling, etc.). Therefore, learning to be awakened or alerted or to assume defensive patterns may involve more than the pertinent general attitude: it may even implicate minor features and precise gestures that individualize one response as different from others of the same kind.

An appropriate incentive may be obtained either from presentation or cessation of a tone: the latter possibility confirms commonplace observations and extends experimental reports (Rowland 1957; Zeleni 1907). Certain units in the auditory system react to substraction of sound, so no special mechanism need be postulated for the elaboration of learned responses to tone cessation (Galambos 1952).

The learning process analyzed here exhibited the main features of classical conditioning (technique, evolution, inhibition, disinhibition, etc.) (Pavlov 1941). Natural absolute stimuli (shock to leg, food, etc.) have occasionally been replaced by direct electrical excitation of nervous tissues, usually with the purpose of placing the locus of learning. These efforts have met either success (dorsal roots, posterior columns, lateral cerebellar lobes, hypothalamus, amygdaloid complex) or failure (ventral roots, sygmoid gyri, hypothalamus) (Ban and Shinoda 1950; Masserman 1941; Miller 1957; Morgan 1951; Roig, Sommer Smith, Galeano and Segundo): the assumption has been made that failure derives from the fact that the stimulation is applied

beyond the area where new connections may be established, i.e., closer to the effector. Application of this criterion suggests that most pathways that issue from stimulated nuclei (CM, MRF) and eventually reach somatic or autonomic effectors do indeed traverse a zone that may be penetrated by freshly formed channels (that emanate from acoustic pathways). The precise locus of the new connection is not placed in the immediate vicinity of the stimulating electrode, since small electrolytic destruction at that level did not modify conditioned responses. One cat exhibited a perturbation in its learned and learning abilities after a relatively large lesion of caudal half of CM: further studies are indicated to confirm and extend this and similar (but scattered) reports on the deleterious effect of subcortical lesions upon conditioned behavior (Deryabin 1946; Fessard and Gastaut 1954; Hernández Peón, Guzmán Flores, Alcaraz, and Fernández Guardiola 1956; Knott, Ingram and Correll 1956; Stellar, Chambers, Live, Levitt and Sprague 1958).

The relationship between learning and brain stem probably goes beyond the simple acquirement of behavioral reactions mediated at that level. Evidence has been reviewed elsewhere suggesting that important steps in the process of conditioning occur therein (Buser and Roger 1957; Fessard and Gastaut 1954; Gastaut *et al.* 1957; Lissák 1956). Moreover, epinephrine influences learned reactions and does so by way of a neural substratum tentatively placed in hypothalamic and/or mesencephalic nuclei (Anokhin 1957). A direct excitation of these areas (sub-threshold for visible effects) facilitates or inhibits reciprocally alimentary and defensive conditioned reflexes and, under certain conditions, improves perceptual discrimination (Fúster 1957; Grastyán, Lissák and Kékesi 1956; Knott, Ingram and Correl 1956).

Certain discriminatory mechanisms remained operational in the presence of behavioral and electroencephalographic sleep and, in many cases, the slumbering animal was capable of a correct choice between stimuli that, in the wakeful condition had been rendered, through training, operant or inoperant. No major impediment existed in the appraisal of "conditioned inhibitory", "delayed" or "extinguished" sounds, which were entirely ineffective or produced partial, brief EEG "activation". Differentiation of separate frequencies (well distinguished by the vigilant animal) encountered greater difficulties and accuracy of discernment depending upon the reaction involved: when exclusively the tone of 200 c/sec. was reinforced, EEG "activation" and behavioral arousal occurred also with "negative" stimuli of up to 250 and 210 c/sec. respectively (the conditioned head turning response appeared only after the positive stimulus). Discrimination between initiation (iT) and cessation (CT) of a tone also was imperfect and even after prolongued training the never reinforced iT continued to produce a brief EEG "activation" in the preparation in which reinforcement came after CT; arousal produced by CT was complete.[1] Little can be said of the precise time relationship between relatively concomitant effects; therefore, the possibility exists that when the stimulus was presented to the slumbering animal, the poorly discriminative (and hence more widely provoked) EEG "arousal" occurred first and, only then and on the basis of this new encephalic condition, the finer differentiations leading or not to behavioral arousal and head turning were rendered possible.

Electroencephalographic changes appeared earlier and subsisted longer than behavioral shifts, confirming that EEG inspection constitutes an invaluable tool in this type of study (Buser and Roger 1957; Fessard and Gastaut 1954; Gastaut *et al.* 1957). On the other hand, a substantially variable performance could take place upon a uniform background

[1] Brief ("phasic") EEG "activation" occurs either when the stimulus is on the verge of losing its arousing capabilities (final stages of habituation, extinction, conditioned inhibition, etc.) or when, though negative, it resembles closely the positive excitation (e.g. tones with small frequency difference, iT and CT) (Sharpless and Jasper 1956) (see Results). In the case of habituation the diencephalic component of the activating system has been considered responsible for this type of response (Sharpless and Jasper 1956): though likely, the hypothesis that a similar substratum participates in the other examples is as yet unsupported by direct evidence.

of EEG "arousal". Hence, recording and observation must necessarily complement each other. When the absolute stimulus is a painful shock, cortical "activation" produced by the conditioned signal may become limited to the sensori-motor area. "Concentration" did not occur in the present series even with many hundreds of trials: this could be due to the use of an unconditioned excitation involving direct energization of di- and mesencephalic structures that produce diffuse effects (Rossi and Zanchetti 1957; Segundo 1956).

Observable performance is but one outcome of brain stem stimulation. Animal experimentation suggests that subjective effects either may be absent (hypothalamus) or, when present, differ from one zone to another involving an emotion akin to fear (tectal area, lateral thalamus), a pleasurable experience (intralaminar nuclei, hypothalamus, etc.) (Cohen, Brown and Brown 1958; Delgado 1952; Delgado, Robert and Miller 1954; Delgado, Rosvald and Looney 1956; Masserman 1941; Miller 1957; Olds 1956). The possibility of conditioning CM and MRF effects, the arousing capabilities of the conditioned tone and the excited (even "neurotic") behavior of the animal in the experimental situation (see Results) support the idea that excitation produced an intense affective state, clearly perceived and remembered. Comments on the experiential aspects of central stimulation and based upon animal experiments must of course remain tentative until tests are performed in un-anesthetized humans.

Repeated application of electrical stimuli to CM or MRF seemed to induce a long-lasting (5-24 hours) decrease in responsiveness. If structures critical for arousal and alerting do indeed exhibit prolonged recovery cycles, such refractoriness may be involved in causing the comparably prolongued attenuation of arousal or alerting that follows repeated application of natural stimuli (Pavlov 1941; Sharpless and Jasper 1956).

SUMMARY

In cats with chronically implanted electrodes, an indifferent tone was reinforced by electrical stimulation of centre median (CM) or of mesencephalic reticular formation (MRF). As a result, the tone per se became capable of producing a behavioral response identical to that of the direct excitation (A head turning, B cowering, C rolling). The process exhibited characteristics of classical conditioning. External and internal (discriminatory, conditioned, delay, extinction) inhibitions could be established.

The conditioned response was associated with generalized EEG "activation" and with evoked potentials in sensory motor cortex, CM and MRF.

During behavioral and EEG sleep, animals retained (with limitations) a "discriminative" capacity that enabled them to be awakened specifically by certain stimuli (novel, "positive") and not by others (indifferent, "negative").

Reinforcement came after cessation of a continuous tone in one cat: eventually it came to respond (both when awake or sleep) to sound substraction but not to sound initiation.

Destruction of the stimulated locus did not modify learned performance; after a large lesion in CM, one cat exhibited a marked depression of its learned and learning abilities.

Results are discussed in relation to literature illustrating the presence of learned mechanisms in the production of basic behavioral responses as arousal, alerting, etc.

RÉSUMÉ

Un ton indifférent fut renforcé, chez des chats ayant des electrodes implantés chroniques, au moyen d'une stimulation électrique du centre médian (CM) ou de la formation réticulaire mésencephalique (MRF). Comme résultat le ton « per se » est devenu capable de produire une réponse de comportement identique à celle de l'excitation directe (A déplacement de la tête, B accroupissement, C roulement). Le processus a démontré les caractéristiques du conditionnement classique. On a pu établir les inhibitions externes et internes (discriminatoires, conditionnées, retard, extinction).

La réponse conditionnée fut associée à une « activation » EEG généralisée, et à des po-

tentiels évoquées du cortex sensori-moteur, du CM et du MRF.

Au cours du sommeil conduite associé à sommeil EEG, une capacité « discriminative » fut retenue (avec limitations) par les animaux de sorte qu'ils ont pu être éveillés spécifiquement par certains stimuli (nouveaux, « positifs »), et non pas par d'autres (indifférents, « négatifs »).

Le renforcissement fut réalisé chez un chat après cessation d'un ton continu: il a répondu, éventuellement (à l'état d'éveil, et à l'état de sommeil) à la soustraction sonore mais non pas à l'initiation sonore.

La destruction du foyer stimulé n'a pas modifié l'accomplissement des actes appris; à la suite d'une lésion large du CM une dépression marquée fut démontrée par un chat au sujet de ses capacités d'apprendre et de ses capacités déjà appris.

On discute les résultats en rapport avec la littérature, en illustrant la présence des mécanismes appris dans la production de réponses de comportement de base, telles que l'éveil, la vigilance, etc.

ZUSAMMENFASSUNG

Bei Katzen mit implantierten Dauerelektroden wurde ein indifferenter Tonstimulus durch elektrische Reizung des Centrum medianum oder der Retikulärformation des Mittelhirns verstärkt. Dies hatte zu Folge, dass der Ton ''per se'' die Fähigkeit erhielt, eine Antwort im Verhalten des Tieres hervorzurufen, welche identisch war mit derjenigen, welche durch direkte Reizung erzeugt werden konnte (A. Kopfdrehung, B. Ducken, C. Rollen). Der Prozess zeigte die üblichen Merkmale eines klassischen bedingten Reflexes. Äussere und innere Hemmungen konnten erzeugt werden (diskriminatorische Hemmung, bedingte Hemmung, Verzögerungshemmung, Auslöschung).

Die bedingte Reflexantwort trat zusammen mit einer allgemeinen ''EEG-Aktivierung'' und mit Reizantwortpotentialen in der sensorischen und motorischen Rinde, im Centrum medianum und in der Retikulärformation des Mittelhirns in Erscheinung.

Während des Schlaf, gekennzeichnet durch charakteristische EEG-Veränderungen, behielten die Tiere eine gewisse, beschränkte Fähigkeit der ''Diskrimination'', welche ihnen ermöglichte, auf gewisse spezifische Reize hin aufzuwachen (neue, unbekannte Reize, ''positive'' Reize), während andere Reize keinen solchen Weckeffekt erzeugten (indifferente Reize, ''negative'' Reize).

Bei einer Katze erfolgte die Verstärkung immer nach dem Abklang eines kontinuierlichen Tones. Schliesslich begann das Tier auf Ton-Beendigung zu antworten und nicht auf Ton-Anfang. Dies erfolgte sowohl im Wach- als auch im Schlaf zustand.

Zerstörung des Reizortes ergab keine veränderung des erlernten Verhaltens. Nach Plazierung einer grossen Läsion im Centrum medianum zeigte eine Katze beträchtliche Verminderung sowohl ihrer erlernten Fähigkeiten als auch ihrer Lernfähigkeit.

Die Befunde werden besprochen in Bezug auf die bestehende Litteratur betreffs der Rolle, welche erlernte Mechanismen in der Ausbildung fundamentaler Verhaltungsweisen wie z.B. Erwachen, Aufmerksamkeitserhöhung u.s.w. spielen.

REFERENCES

ANOKHIN, P. K. Role of the reticular formation in various forms of higher nervous activity. *J. Physiol.*, USSR, **1957**, *43*: 1072-1085.

BAN, T. and SHINODA, H. Cited by PATTON, H. D. in Visceral functions of the nervous system. *Ann. Rev. Physiol.*, **1958**, *20*: 509-532.

BUSER, P. et ROGER, A. Extrait du volume publié à l'occasion du IVe Congrès International d'Electroencéphalographie et de Neurophysiologie Clinique et de la VIIIe Réunion de la Ligue Internationale contre l'Epilepsie. **1957**, 21-28 juillet, Bruxelles, p. 417-444.

COHEN, B. D., BROWN, G. W. and BROWN, M. L. Avoidance learning motivated by hypothalamic stimulation. *J. exp. Psychol.*, **1958**, *53*: 228-233.

COLLIAS, J. C. and MANUELIDIS, E. E. Histopathological changes produced by implanted electrodes in cat brain. Comparison with histopathological changes in human and experimental puncture wounds. *J. Neurosurg.*, **1957**, *14*: 302-328.

DELGADO, J. M. R. Responses evoked in waking cat by electrical stimulation of motor cortex. *Amer. J. Physiol.*, **1952**, *171*: 436-446.

DELGADO, J. M. R., ROBERTS, W. W. and MILLER, N. W. Learning motivated by electrical stimulation of the brain. *Amer. J. Physiol.*, **1954**, *179*: 587-593.

DELGADO, J. M. R., ROSVALD, H. W. and LOONEY, E. Evoking conditioned fear by electrical stimulation of subcortical structures in the monkey brain. *J. Comp. Physiol. Psychol.*, **1956**, *49*: 373-580.

DERYABIN, U. S. The influence of the damage of thalami optici and hypothalamic region upon the higher nervous activity. *J. Physiol.*, USSR, **1946**, *32*: 533-548.

FESSARD, A. et GASTAUT, H. Corrélations neurophysiologiques de la formation des réflexes conditionnels. Dans Le conditionnement et l'apprentissage, Symposium de l'Association psychologique scientifique de langue française. **1954**, Puf, Paris.

FUSTER, J. M. Tachistoscopic perception in monkeys. *Fed. Proc.*, **1957**, *16*: 43.

GALAMBOS, R. Microelectrode studies on medial geniculate body of cat. III Response to pure tones. *J. Neurophysiol.*, **1952**, *15*: 381-400.

GASTAUT, H., JUS, A. et C., MORRELL, F. et STORM VAN LEEUWEN, W., DONGIER, S., NAQUET, R., REGIS, H. et ROGET, A., BEKKERING, D., KAMP, A. et WERRE, J. Etude topographique des réactions électroencéphalographiques conditionnées chez l'homme. *EEG Clin. Neurophysiol.*, **1957**, *9*: 1-34.

GRASTYÁN, E., LISSÀK, K. and KÉKESI, F. Facilitation and inhibition of conditioned alimentary and defensive reflexes by stimulation of the hypothalamus and reticular formation. *Acta Physiol. Acad. Sci. Hungar.* **1956**, *9*: 133-151.

HERNÁNDEZ PEÓN, R., GUZMÁN FLORES, C., ALCARAZ, M. and FERNÁNDEZ GUARDIOLA, A. Functional role of brain stem reticular system in salivary conditioned response. *Fed. Proc.*, **1956**, *15*: 91-92.

HESS, W. R. *Hypothalamus and Thalamus.* **1956**, Stuttgart, Georg Thieme Verlag. p. 70.

JOUVET, M. et HERNÁNDEZ PEÓN, R. Mécanismes neurophysiologiques concernant l'attention, l'habituation et le conditionnement. (In Fischgold, H. et Gastaut, H. Conditionnement et Réactivité en *Electroencéphalographie*, **1957**, Paris, Masson, p. 39-49).

KNOTT, J. R., INGRAM, W. R. and CORRELL, R. E. Diencephalic influences on performance. *EEG Clin. Neurophysiol.*, **1956**, *8*: 524.

LISSÁK, K. Die Rolle der subkortikalen Mechanismen bei den bedingten Reflexen. *Zeitschrift für ärtzliche Fortbildung.*, **1956**, *50*: 338-342.

MASSERMAN, J. M. Is the hypothalamus a center of emotion ? *Psychosom. Med.*, **1941**, *3*: 3-25.

MILLER, N. E. Experiments on motivation. *Science*, **1957**, *126*: 1271-1278.

MORGAN, C. T. The psychophysiology of learning. (In Stevens, S. S. *Handbook of Experimental Psychology*, **1951**, New York, John Wiley. p. 1936).

MORUZZI, G. and MAGOUN, H. W. Brain stem reticular formation and activation of the EEG. *EEG Clin. Neurophysiol.*, **1949**, *1*: 455-473.

OLDS, J. A preliminary mapping of electrical reinforcing effect in the rat brain. *J. Comp. Physiol. Psychol.*, **1956**, *49*: 281-285.

PAVLOV, I. P. *Lectures on Conditioned Reflexes.* **1941**, New York, International Publishers, 3rd. ed., vol. I. p. 414, vol. II. p. 199.

PROSSER, C. L. and HUNTER, W. S. The extinction of startle responses and spinal reflexes in the white cat. *Amer. J. Physiol.*, **1936**, *117*: 609-618.

ROIG, J. A., SOMMER SMITH, J. A., GALEANO, C. and SEGUNDO, J. P. (Preliminary observations).

ROSSI, G. F. and ZANCHETTI, A. The brain stem reticular formation. Anatomy and physiology. *Arch. Ital. Biol.*, **1957**, *95*: 203-435.

ROWLAND, V. Differential electroencephalographic response to conditioned auditory stimuli in arousal from sleep. *EEG Clin. Neurophysiol.*, **1957**, *9*: 585-594.

SEGUNDO, J. P. The reticular formation. A survey. *Acta Neurol. Latinoamer.*, **1956**, *3*: 245-281.

SEGUNDO, J. P., ARANA, R. and FRENCH, J. D. Behavioral arousal by stimulation of the brain in the monkey. *J. Neurosurgery*, **1955**, *12*: 601-613.

SHARPLESS, S. and JASPER, H. H. Habituation of the arousal reaction. *Brain*, **1956**, *79*: 655-680.

STELLAR, E., CHAMBERS, W. W., LIVE, C. N., LEVITT, M. and SPRAGUE, J. M. Behaviour of cats with chronic reticular and laminar lesions. *Fed. Proc.*, **1958**, *17*: 156.

ZÉLENI, G. P. Cited by PAVLOV, I. P. *Lectures on Conditioned Reflexes.* **1941**, New York, International Publishers, 3rd. ed. vol. I. p. 414.

Reference: SEGUNDO, J. P., ROIG, J. A. and SOMMER-SMITH, J. A. Conditioning of reticular formation stimulation effects. *EEG Clin. Neurophysiol.*, **1959**, *11*: 471-484.

PRINTED IN CANADA

DEFENSIVE CONDITIONING OF ELECTROGRAPHIC AROUSAL WITH DELAYED AND DIFFERENTIATED AUDITORY STIMULI [1]

HENRY GLUCK, Ph.D. and VERNON ROWLAND, M.D.[2]
Division of Psychiatry, School of Medicine and
Department of Psychology, Western Reserve University, Cleveland, Ohio

(Received for publication: December 8, 1958)

INTRODUCTION

Electrophysiological recording during conditioning has been reviewed recently by Gastaut (1958), Morrell and Jasper (1956), and Rusinov and Rabinovich (1958). In general, investigations have dealt with the distributions of evoked potentials (Jouvet and Hernández-Peón 1957), changes in induced rhythms (John 1959; Yoshii and Hockaday 1958), and in distributions of the more endogenous frequencies (Morrell and Jasper 1956). The earlier studies (Jasper and Shagass 1941) demonstrated that electrical activation could be conditioned according to the general laws described by Pavlov (1927). More recently attention has been directed to questions regarding the formation of the "temporary" connections in the brain. Problems regarding the locus and electrical signs (Morrell and Jasper 1956; Gastaut 1958) of these connections have been of major interest. The spatio-temporal pattern of the connection formation process has also received attention in the studies by John (1959) and Yoshii and Hockaday (1958).

In a recent study Rowland (1957) made the incidental observation that the differentiated stimulus seemed to enhance synchronous activity in the electrographic records of sleep-deprived animals observed under conditioning programs. Gastaut (1958) and Alexander (1958) have emphasized slow activity in association with inhibition. The present work relates Pavlovian inhibition and excitation with patterns of electrographic response (arousal) developed in defensive conditioning of sleeping animals. The hypothesis which stimulated these experiments was that the inhibition of delay and the inhibitory effect of a differentiated conditioned stimulus would be demonstrated by synchrony patterns in the electrographic response.

METHOD

Each of 3 cats was prepared with 8 permanently implanted electrodes located in the following way. Extradural: bilaterally on the anterior lateral gyri; bilaterally, on the ectosylvian gyri. Stereotaxic subcortical placements: medial geniculate nucleus, mesencephalic tegmentum, centralis medialis, and hippocampus. Extradural leads were short silver coils 1-2 mm. in diameter, and deep leads were lucite-insulated white steel insect pins with 0.1 to 0.2 mm. exposed tips. All records were monopolar and referred to a small skull screw located in the anterior portion of the frontal sinus. In a pilot study, recording between two screws in this location, 8 mm. apart, revealed minimal activity, the largest potentials not exceeding 20 μV.

A month following surgery the animals were acclimated to (1) permanently worn harnesses bearing electrodes for delivery of shocks across the shoulders; (2) daily feeding in the experimental cage; (3) sleep deprivation by limiting sleep at night (Rowland 1957), and (4) spending 2-3 hours after the feeding in the experimental cage, which was located in an isolated, dimly-illuminated recording room. Precautions were taken in the programming to eliminate all extraneous cues such as equipment noise occurring before or during the test periods.

The conditioned stimulus (CS) was a 2/sec. click, the differentiated stimulus (DS), a 200 c/sec. tone, and the unconditioned

[1] Supported in part by the Cleveland Foundation.
[2] Work done as part of a career-investigator grant of the National Institute of Mental Health.

stimulus (US), a 60 c/sec. 1-8 mA monitored current of 1/2 sec. duration, delivered from a 750-V. transformer through a capacitive impedance (.03 mfd) to the harness electrodes. These made contact with skin through non-drying glycerine-saline soaked gauzes. With this method, changes in electrode-skin resistance were small compared to that in the shocking circuit and did not appreciably alter the current actually passed. Shock intensity was governed by selecting that value for each cat that produced an unconditioned response of moderate jerking of the body and no more. This value ranged from 1-6 mA. Auditory stimuli were delivered by a loudspeaker mounted on the experimental cage and were held constant in intensity throughout the entire experiment. The differentiated stimulus was subjectively louder than the conditioned stimulus to rule out brain wave changes resulting from mere reduction of intensity of the differentiated stimulus.

The experiment was conducted in four parts (cf. table I) with 5 days of control and adaptation before beginning conditioning. This control consisted of 2-min. presentations of the 2/sec. click stimulus, applied 10 times per daily session, trials randomized around a mean inter-trial interval of 8 minutes.

TABLE I

Summary of Training Programs

Program I.
CS and US given with daily increases in CS-US interval to a maximum of 120 sec.
Program II.
A. DS given only.
B. DS given 5 times per session, CS and US given 5 times per session. Separate applications in random order.
Program III.
A. DS presented in first 30 sec. of CS. US still applied.
B. DS presented from 60th to 80th sec. of CS. US still applied.
Program IV.
A. DS presented during terminal 20 sec. US withheld.
B. Same as III B, except US withheld.

Program I. Following the procedure recommended by Pavlov (1927) the delayed conditioning was developed by slowly increasing the CS-US interval, day by day, from an initial 5 sec. to a final 120 sec. by alternating daily increments of 5 and 10 sec. Ten trials were given daily with random inter-trial intervals (mean, 8 min.) as in control period. The CS-US interval of 2 min. was reached by the 16th day and held constant for 6 days.

Program II. For 5 days (10 trials per day) the animals were given 200 c/sec. tones of 20 sec. duration with no reinforcement following the end of the tone (DS). For a subsequent 9 to 13 day period they were exposed to the DS 5 times daily, interspersed randomly with the CS, also given 5 times.

Program III. The DS was now superimposed at various times during the presentation of the CS, the latter remaining clearly audible to the experimenter. These stimuli were also presented individually. There was one test trial a day presenting the 20-sec. DS early in the CS (within 20 sec. after onset — program III A). Later in this program the DS was presented in the middle of the CS-US interval (60-80 sec. after onset, program III B). This procedure, one of the standard tests used in classical conditioning for the measure of inhibitory effect of stimuli, also served as a control for later use of the DS in a different context (program IV). Ten days were devoted to this form of testing. The DS could not be too frequently applied in combination with the CS because of the possibility of its becoming a secondary conditioned stimulus.

Program IV. For 15 days, if the DS was presented during the CS, the shock was withheld. If the DS was not presented during the CS, the trial was reinforced as usual by shock. Under these conditions there were one to three reinforced trials during any one day. The first 10 days of this program had the DS applied during the terminal 20 sec. of the CS. The last 5 days had the combination occurring from the 60th to 80th sec. of the CS. A few tests were made subsequently of the combination occurring during the first 60 sec. of the CS.

The amplifiers of the EEG machine were blocked by the shock stimulus for 5 to 10 sec. after the end of the stimulus, but the 60 c/sec. stimulus artifact was eliminated by being grounded by telephone relays.

Deep placements were checked by histology and surface placements by post-mortem examination of calvarium and brain. Integrity of insulation on deep electrodes was tested post-mortem by passing a 6-V. direct current through the electrode used as a cathode and observing for gas formation in saline.

RESULTS

General description of the behavior. None of the cats showed any resistance to being placed in the experimental cage throughout the experiment. This was the only place they were fed so that in spite of the occasionally painful conditions of the experiment, they did not generalize negatively to the environment. They ate well and maintained their body weights throughout the four months of the experimentation.

Development of the delayed conditioning. Preliminary observations of the development of the delayed conditioning were made in a brief report elsewhere (Rowland 1959) and are not repeated here. During the control period the animals after habituation to the click stimuli, showed no identifiable consistent pattern of electrographic response.

The CS evoked only conditioned desynchronization until the 10th day when the CS-US interval had been expanded to 75 sec. At this time a period of slow waves began to appear in the first part of the CS and increased until by the 22nd day a characteristic pattern was well established. The daily mean length of slow rhythms during the CS is plotted for each cat in figure 1. The reduction occurring at the 20th day in cats A-2 and A-3 was produced by increasing the intensity of the US. Cats A-2 and A-3 tended toward more synchrony during the CS than did A-1, this being reflected in the difference in shock levels needed for optimal response: 2-4 mA. for A-2; 3-6 mA. for A-3; and 1-2 mA. for A-1.

The synchrony during the CS was enhanced by (1) reducing intensity of the US (Rowland 1959), (2) by a deep level of sleep (i.e. by EEG criteria) at the time a trial was given, and (3) by a sufficient repetition of trials in a session.

Almost invariably the appearance of the synchronous record followed a particular time

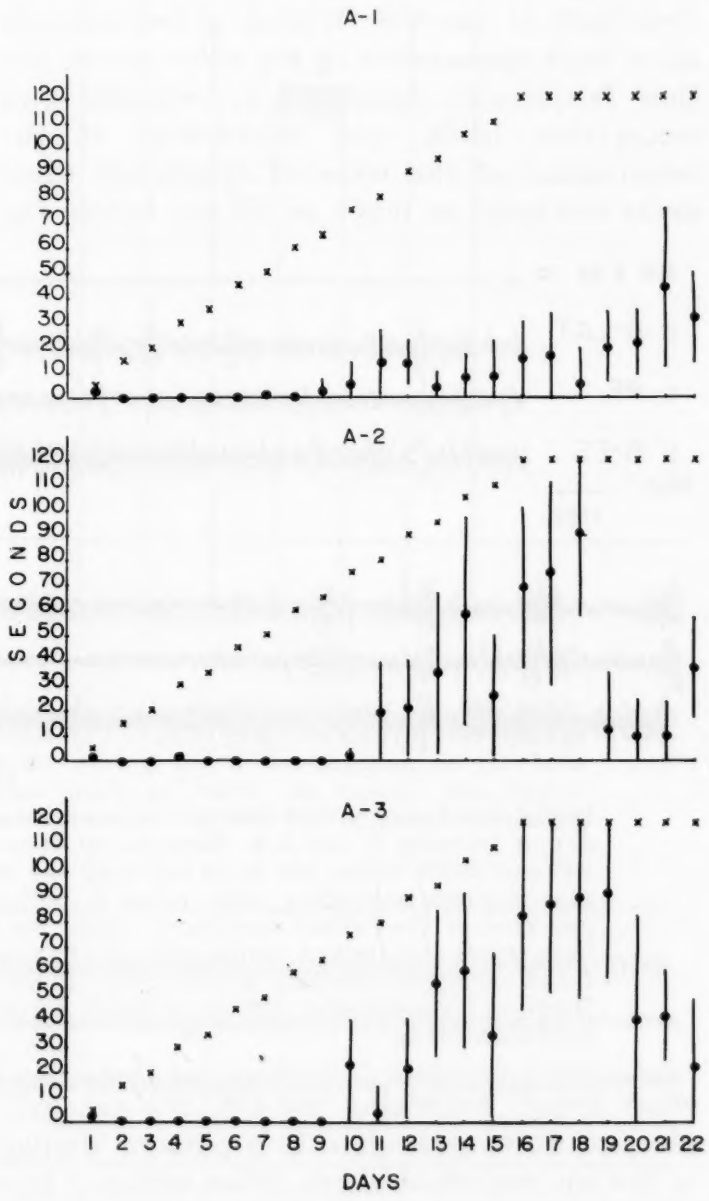


Fig. 1

Daily mean duration of initial synchrony period for each cat for the first 22 days of conditioning. The crosses represent the duration of the conditioned stimulus, and the dots the corresponding mean duration of the synchrony response. The vertical lines are an estimate of variation of synchrony response for each day (2.5 times the expected value of the standard deviation of the mean above and below the mean duration of synchrony). The sudden drop in duration of synchrony on the nineteenth and twentieth days for cats A-2 and A-3 is due to an increase in intensity of the US.

sequence with regard to loci of the electrodes (fig. 2). After the initial arousal the lateral gyri were the first to show a crescendo return of slow frequencies (3-6 c/sec.) and spindling, and the last to activate in the final arousal period. Even in those occasional trials where low voltage fast activity persisted throughout the CS in some leads, the lateral gyri still showed slow rhythms and spindling in the first half of the CS. Within a few seconds after their appearance in the above areas, the slow frequencies developed in reticular and ectosylvian leads, and conversely, at the termination of the wave of synchrony these areas activated as much as 10 sec. before the

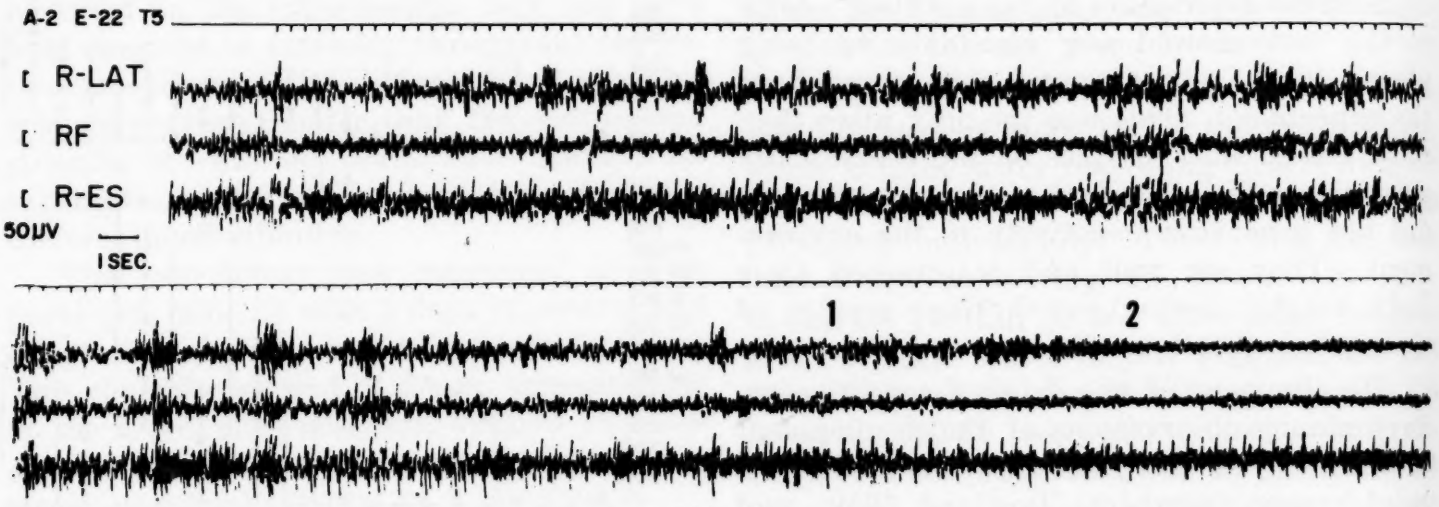


Fig. 2

Initial synchrony period during two-minute conditioned stimulus in the fifth trial on the 22nd day of training in cat A-2. Records continuous. At point 1, desynchronization is apparent in RF and R-ES leads, but in R-Lat lead the high voltages are only somewhat attenuated, the slow rhythms persisting until point 2, indicating spatio-temporal distribution of the disappearance of the initial synchrony. Note the accentuation of evoked potentials in the R-ES leads when the arousal period sets in. Legend for this and all following figures: R-Lat and L-Lat = right and left lateral gyri; R-ES and L-ES = right and left ectosylvian gyri; Hipp = hippocampus; RF = reticular formation; MG = medial geniculate nucleus; CA = caudate nucleus.

other areas. Following the US, the synchronization developed again in a pattern similar to the one described above, often within a few seconds.

The hippocampus showed 6/sec. theta activity (Green and Arduini 1956) replacing slow, high voltage activity (undifferentiable from synchronized activity in other leads) when the two electrographic arousal periods to the CS developed. With full arousal, the hippocampus on some occasions also showed low voltage fast activity.

Differentiation of the tone. After habituation and once some stability of response had been established, the most frequent pattern of response to the DS was an initial activation followed by a slow return to synchrony. Frequencies and distributions of slow activity were very similar to those observed with the CS. This type of response was characterized as a "standard" response to the DS. A "standard" response to the CS was identified by an initial arousal period, followed by first a synchrony period, then a terminal arousal period during the stimulus. Figure 3 shows the percentage of "standard" responses to both the DS and CS for the last four days of differential conditioning (program II) for each animal. At this time the conditioned response to the CS was increased in stability in comparison to the earlier conditioning. Cat A-1 showed the best differentiation, which was unexpected since it tended to show the least amount of slow activity during the CS. A-1 established the differentiation sooner, since by the ninth day it was showing 100 per cent "standard" responses, whereas A-3 did not reach this level until the twelfth day and A-2 never showed more than 80 per cent "standard" response.

Application of the DS during the CS. A total of 7 applications of the differentiated stimulus for all cats was made in the initial

synchrony period of the response to the CS. In every instance there was a slight desynchronization which was followed by further synchronization without disruption of the second arousal period (fig. 4). All cats had a total of 21 applications of the DS during the final arousal period (approximately 60 sec. after the onset of the CS). In 6 instances (all occurring in cat A-3) there was a suggestion of an "induced" synchrony during this combined application of CS and DS, but its appearance was not reliably reproduced.

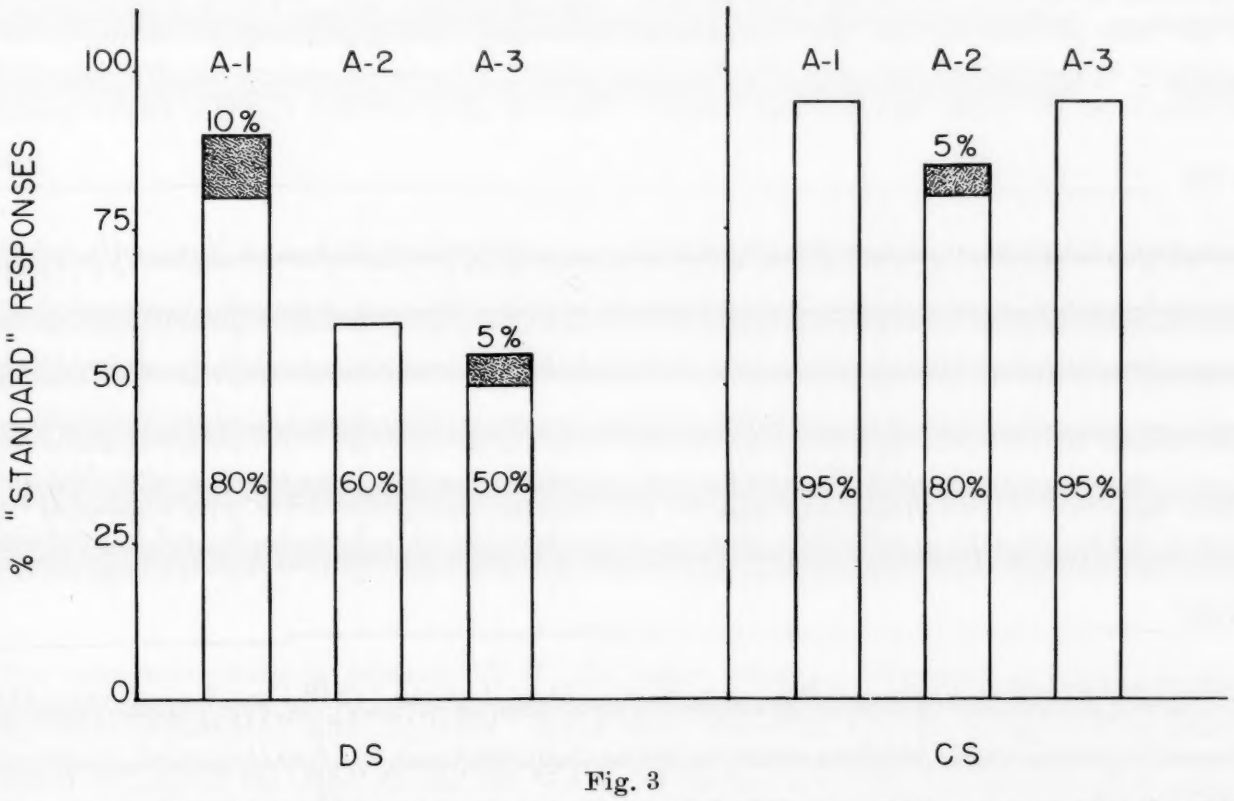


Fig. 3

Per cent of total trials in which there were "standard" (see text) responses to the DS and CS. Data from the 40 final trials for each cat during the differentiation of the tone (program II). The stippled areas represent those trials in which the record was desynchronized before the onset of the auditory stimulus with "standard" response occurring nevertheless.

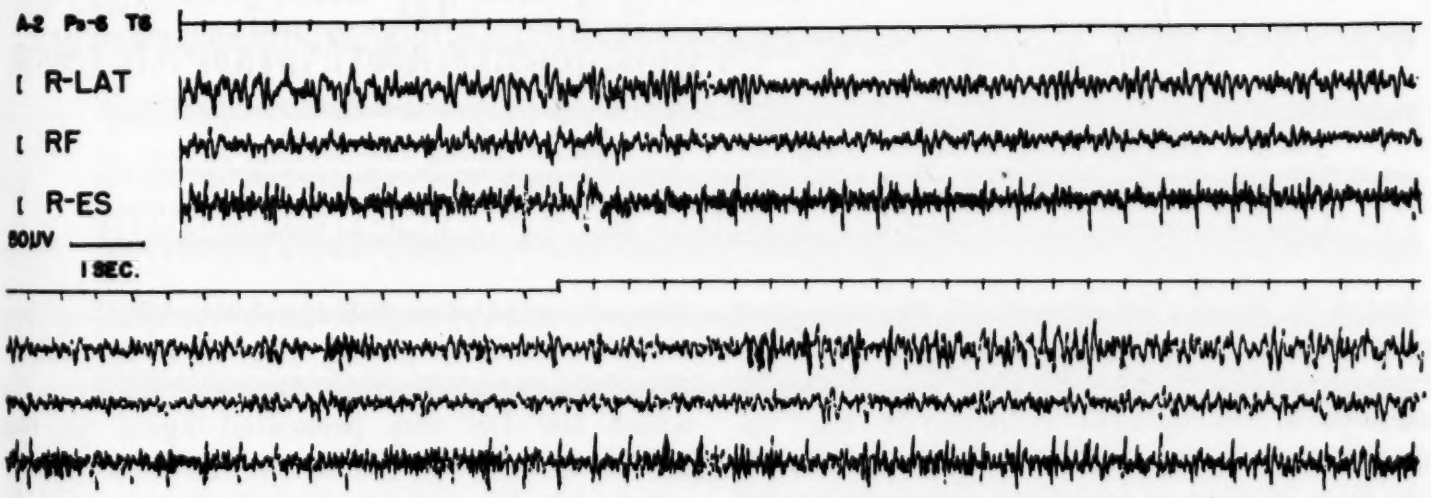


Fig. 4

40-sec. sample of the standard 2-min. trial taken from the first minute of CS. The sustained depression of the signal line indicates the superposition of the DS during which the click stimulus continues. These trials (program III A) were reinforced. Background shows a strong synchrony response which is partially desynchronized by the DS, especially in right ectosylvian record. Synchrony resumes after DS and illustrates the resistance to sustained disturbance by the DS. Remainder of response (not shown) underwent characteristic transition to desynchronized activity in second minute. Records continuous.

Thus, the duration of the synchrony response to the CS was not altered by the DS, and also the DS did not reliably induce synchrony once the record was activated during the second arousal to the CS.

The differentiated stimulus applied to indicate no shock after CS. With the DS applied during the last 20 sec. of the CS (program IV A), a new appearance of synchrony developed within 5 to 10 trials in each cat, beginning 5 to 15 sec. after onset of the tone and continuing to its termination (fig. 5). By the seventh day, after 40 trials, the 3 animals showed 80-100 per cent incidence of this "induced" synchrony. After moving the tone to the first portion of the desynchronized period (program IV B, from 60th to 80th sec. of the CS) we found the synchronous activity was induced within 1-3 trials after the change in all three cats (fig. 6, 7). The slow activity persisted beyond the end of the tone for 5 to 15 sec. and then gave way to the sustained desynchronization characteristic of the final period of the conditioned response. In 5 subsequent days, consisting of an average of 30 further tone-presentation trials for each cat, the response was present respectively in 66 per cent, 80 per cent, and 100 per cent of the trials. Presentation of the CS alone (which served as a control for the above paradigms) showed no presence of synchrony during the second activation period (fig. 6) in a total of 43 trials for all 3 cats. During test runs in which the DS was presented again in the initial synchrony phase the pattern of response was the same as during program III A. The tone desynchronized the record briefly; synchrony returned, but the second arousal still developed as before. The DS-induced synchrony response was completely removed

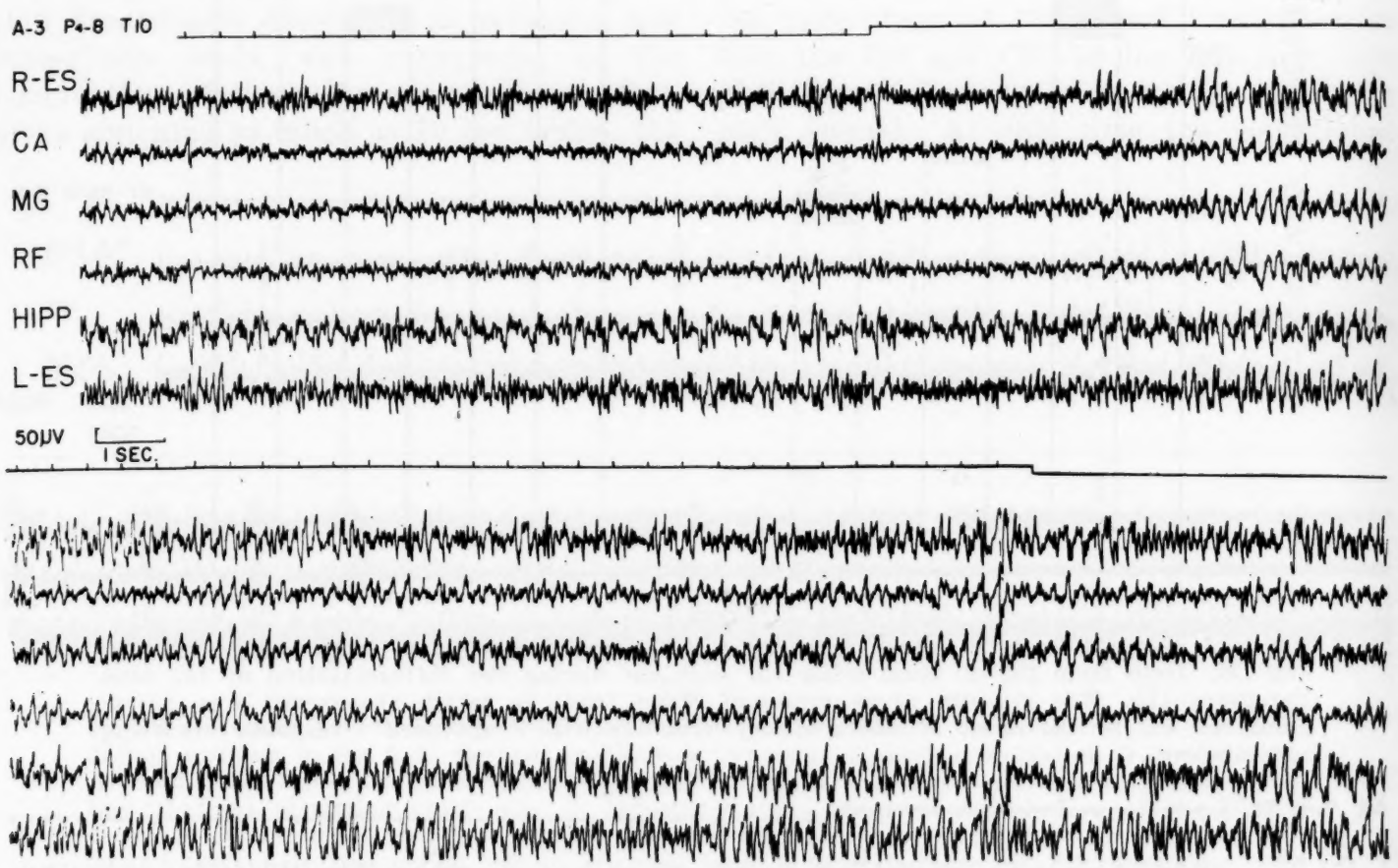


Fig. 5

The DS, now signalling no shock (program IV A), applied during the terminal 20 sec. of the delayed CS, is indicated by the sustained elevation in signal line. The clicking of the CS continues throughout and co-terminates with the DS. Note the marked return of synchrony within 5 sec. of onset of the DS. Records continuous.

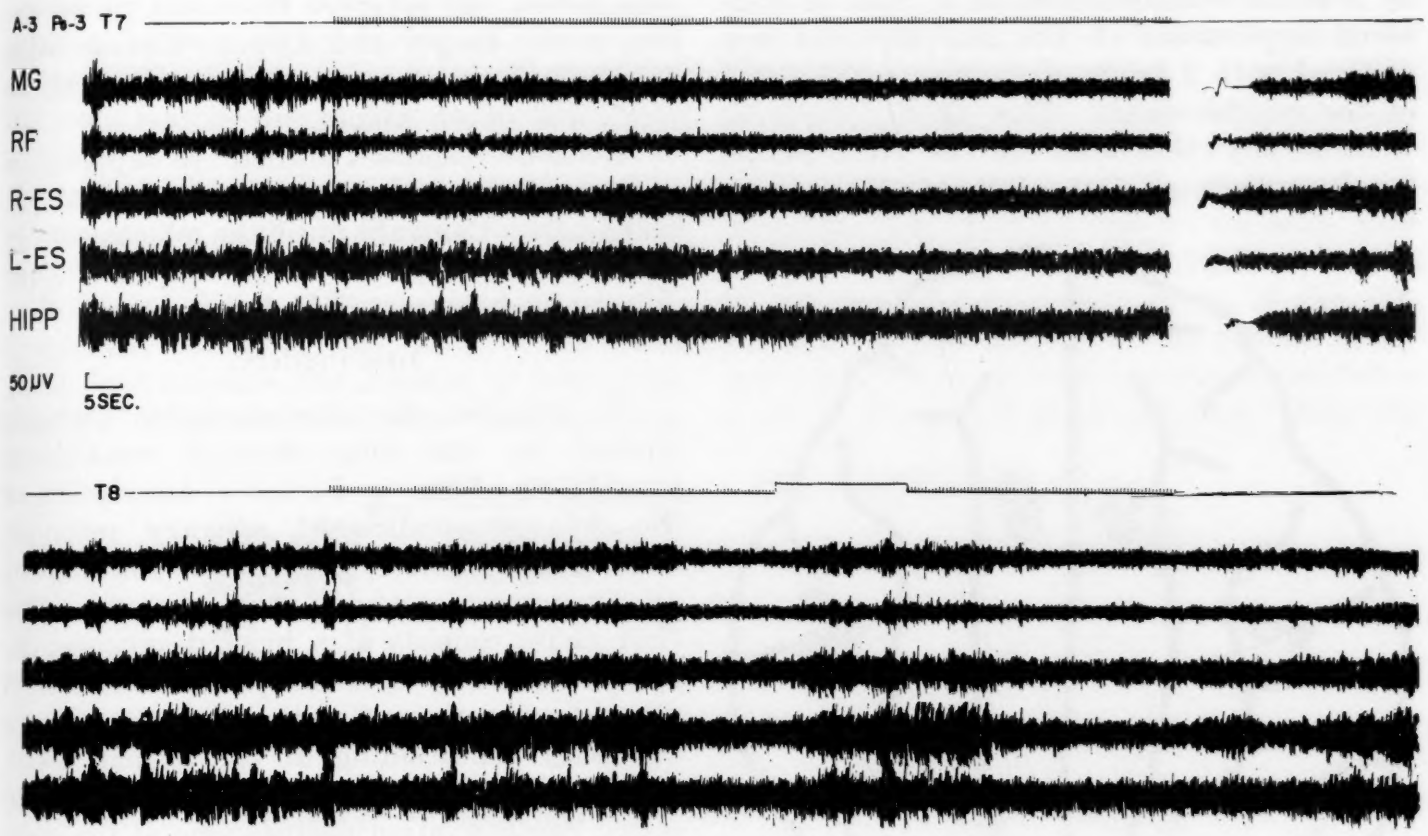


Fig. 6

Two consecutive trials in program IV B. The upper record is "standard response" to reinforced CS; no DS added. Initial synchrony ends approximately midway in the CS with activation supervening until the shock. In the lower record the DS, now a signal of nonreinforcement, is applied early in desynchronized period of response to CS. Slow activity returns within 10 sec. of the onset of the DS, lasting to 15 sec. after its termination. Note slow time base. The 2-min. CS on signal line is immediately followed by an unregistered US indicated by blank space, during which there is no interruption in time (upper record).

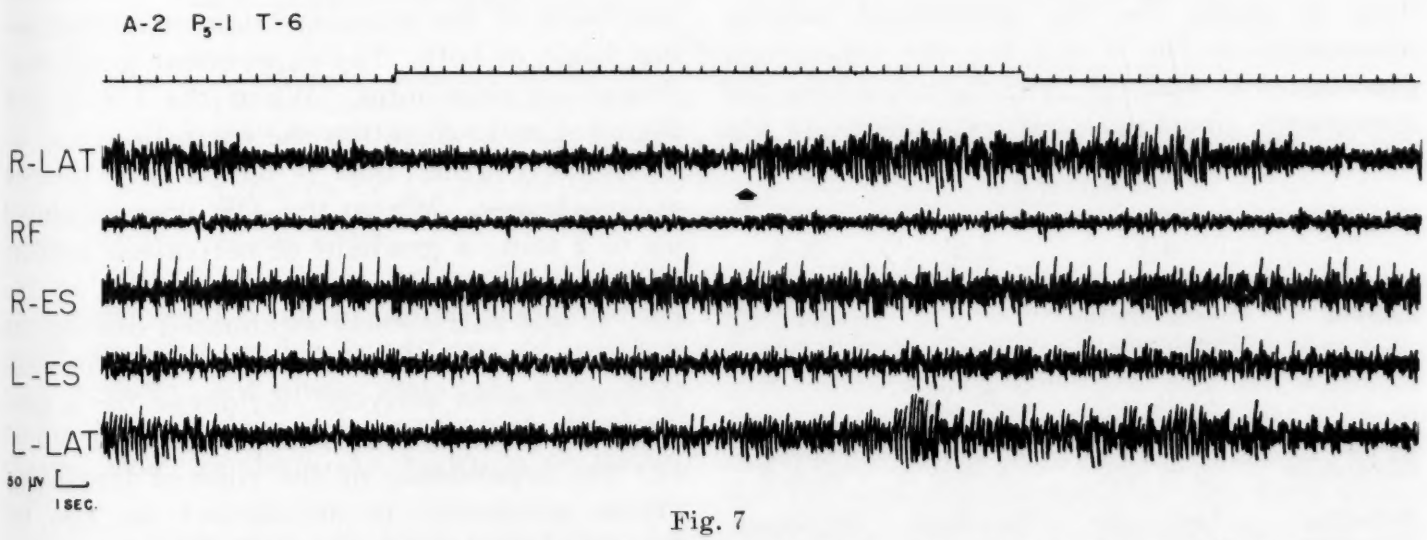


Fig. 7

40-sec. sample showing application of DS early in second arousal period of CS (US withheld, program IV B). Upward elevation of signal line indicates application of tone (DS) during clicks (CS). Record has begun to desynchronize before onset of tone. At about 10 sec. (arrow) synchrony returns to lateral gyri. Note later and less prominent synchrony in ectosylvian gyri and RF. Approximately 10 sec. after end of tone the activation response to the CS returns.

by a single reinforcement of a trial of combined application of CS and DS and was restored with 2 trials of further withholding of the reinforcement. This change occurred without any alteration in the first period synchrony related to the delayed CS.

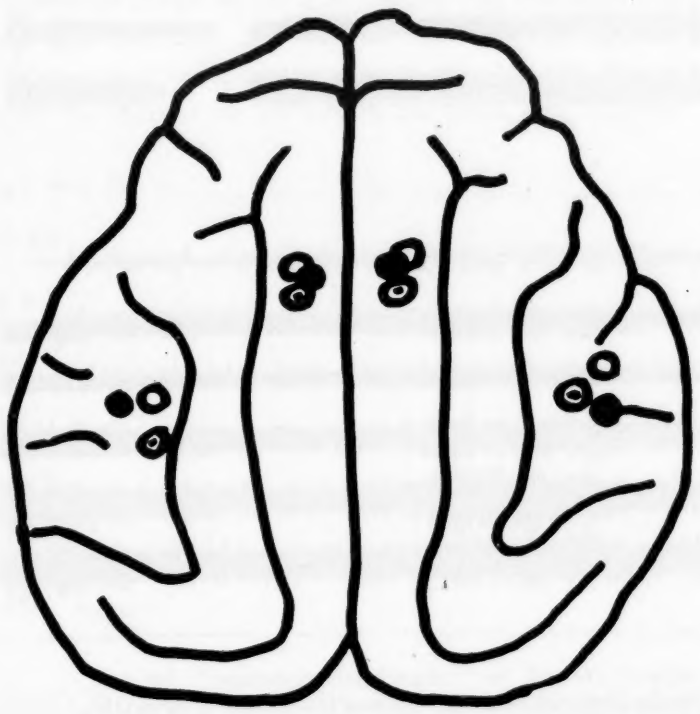


Fig. 8

Loci of extradural placements. Open circles = cat A-1, filled circles = cat A-2, circles with dots = cat A-3.

Postmortem localization of electrode positions is shown for the extradural cortical placements in fig. 8 and for the subcortical placements in table II. The figures giving the stereotaxic coordinates of the electrode tip localization (as referred from the tissue section to the Jasper and Ajmone-Marsan atlas, 1954) indicate respectively the frontal, lateral, and depth planes.

Evoked responses failed to appear in several placements which were verified histologically. Centralis medialis placements in A-1 and A-2 referred to in the text apply only to their stereotaxic placement.

TABLE II

	A-1	A-2	A-3
Hippocampus	Region of fornix joining 2 hippocampal masses 4, 10, +5	On target 2, 8, +3	Penetrates underlying cortex 2, 7, +4
Medial Geniculate	On target 7, 8, +1	On target 4, 8, 0	On target 4, 8, 0
Reticular formation	Just under superior colliculus 3, 2, +2	On target 4, 2, 0	On target 4, 2, 0
Centralis medialis	Lost	Lost	In fundus caudati 14, 3, 0

DISCUSSION

In general, the electrographic patterns elicited by the long delayed conditioned stimulus conform to Pavlov's description of the delayed conditioned salivary response, that is, an inhibitory first phase followed by an excitatory second phase (fig. 9). The first phase consists of a brief desynchronization followed by synchrony, and the second phase by a return of activation. In delayed (10 sec.) conditioning of the human EEG, Motokawa and Huzimori (1949) also describe two activation periods, one at the onset and one at the end of the CS. This pattern appears in the present study even though we worked with moderate pain as the unconditioned stimulus.

The gradual development of a period of synchrony during the increasingly extended conditioned stimulus was due to an elaboration of response related either to simple repetition of the training trials or to increasing delay, or both. The experiment is not conclusive on this point. When the CS is less than 1 min. in duration the excitation may be sufficiently great that it blocks any process of synchrony. When the CS was extended up to 2 min., a gradient of activation became apparent, increasing toward the end of the CS. It was sufficiently attenuated during the first minute to allow a progressive increase in synchronous activity. Evidence for a gradient of activation resides in the following: (1) the dependence of the time of transition (from synchrony to activation) on the intensity of the US (fig. 1); (2) the remarkably smooth progressive diminution in voltage and increase in frequency over many seconds seen in many trials; and (3) the progressive involvement of more areas of the brain in desynchronized activity (fig. 2).

Beck, Doty, and Kooi (1958) noted only occasional slow activity during extinction and unduly prolonged training sessions. This low incidence may be due in part to the brevity of their CS (2 sec.). Under the circumstances of the present experiment, a 5 to 10 sec. latency was frequently found in the appearance of the higher voltage slow activity related to the inhibition of delay (120 sec.) and of the differentiated stimulus (20 sec.). They also noted, in 3 animals, the absence of behavioral response when cortical slow activity was evoked by the CS. They found their animals could respond under conditions of cortical slow activity but these instances were rare and some took place in animals given chlorpromazine and Nembutal in addition to bulbocapnine.

The appearance of two activation responses suggests that the first and briefer one is related to processes of identification of the signal (orientation) and development of an inhibition process identifiable by the synchrony during the first half of the CS. The second, more sustained one is considered related to preparation and defense against the US.

In the development of the differentiation we were unable to eliminate brief desynchronization at the onset of the differentiated stimulus. This pattern was at variance with the previous work (Rowland 1957) in which no arousal appeared with onset of the differentiated tone. However, the present study was carried out during continual reinforcement of the conditioned response while the animals in the earlier work were tested entirely during extinction. This difference suggests a continuing generalization of the initial activation response to the CS in the present experiment. This phenomenon persisted when the DS was superimposed on the first phase synchrony response to the CS, but did not otherwise alter it.

Synchrony developing with delay and differentiation is consistent with a concept of an active process tending to maintain sleep which is manifested in direct proportion to

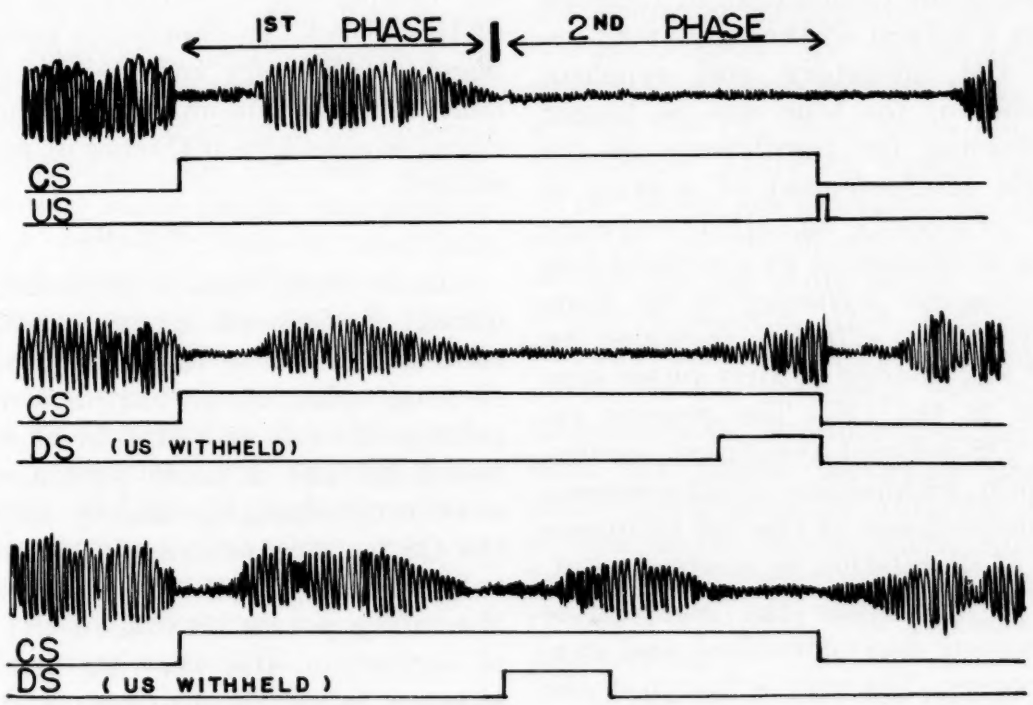


Fig. 9

A schematic summary of the characteristic response patterns to three of the paradigms. The amplitudes and frequencies are grossly exaggerated with respect to the time base. The first line illustrates effect of delay (program I), the second, of differential stimulus signalling no shock (program IV A), and the third, of moving the differential stimulus (program IV B). The summary pertains particularly to the records from association cortex.

(1) the degree of sleep privation, (2) the remoteness in time from the stress (prolongation of the CS-US interval) and (3) the mildness of the stress.

The rapid acquisition of the synchrony response to the DS in the later programs of the experiment points to the new endowment of the stimulus as a signal of non-reinforcement, carrying with it the capacity to induce synchrony even in the face of a competitive desynchronization. The return of desynchronization with the continued conditioned stimulus following the termination of the tone is construed as a return of the excitatory response when the inhibitory and synchronogenic influence of the tone was no longer in effect. Reversing the significance of the DS by a single reinforcement of a trial in which the DS ordinarily signalled non-reinforcement, was accompanied by a prompt loss of the synchronogenic influence of the tone. The specificity of this effect is indicated by the absence of any change in first phase synchrony related to the CS. The prompt recovery of the DS-induced synchrony, accomplished by again withholding reinforcement, confirms the dependence of the DS influence on the nature of its relation to reinforcement.

We wish to emphasize the competitive interaction between desynchronized and synchronized responses. Not only is it seen in the temporal patterns discussed above, but also in spatial patterns as represented by different recording points. The patterns of electrographic desynchronization seen in reticular and auditory cortical leads, along with hippocampal theta, contrasts markedly with the strong tendency of association cortex to lead in the development of synchronous response and be last in desynchronization.

These observations touch on the problems of active versus passive processes in development of sleep. Kleitman (1939) and Bremer (1954) have emphasized the importance of the arousing systems and criticized the Pavlovian description of irradiating inhibition and Hess' (1954) electrically stimulated sleep. Their emphasis is on the fatigue of an arousal system rather than its active inhibition by other systems. Our data suggest that an active competition with excitatory processes can be demonstrated provided excitation is not too great (i.e. long CS and low intensity US) and the need for sleep is great. A synchronogenic influence may also be demonstrated by a stimulus (e.g. DS) if it is associated with reduced excitation (i.e. signals absence of shock). The method we used removes the objections to the use of lesions, drugs, or intracranial stimulation as an unphysiological approach, reveals a stimulus-bound limitation of the active inhibitory influence, and clarifies the competitive circumstances for elicitation of this effect. In short, our position is: hypnogenic inhibitory influences can readily be demonstrated but only in the context of reduced competitive influence of arousing mechanisms.

SUMMARY

1. In three cats, a delayed (2 min.) auditory conditioned stimulus associated with moderate shock to the skin, produced in the electrographic sleep record a characteristic pattern of: (*a*) an initial brief activation followed by (*b*) a more prolonged period of synchrony, changing usually midway through the CS to (*c*) a return of activation enduring to the delivery of the unconditioned stimulus. Recording points leading in the development of activation and showing the greatest resistance to synchrony were auditory cortex, reticular formation, and hippocampus. Points showing the reciprocal predominance of synchrony and resistance to activation were in association cortex.

2. The degree and duration of synchrony present during the first half of the CS varied inversely with the intensity of the US and directly with the progression of trials in a given daily session. Synchrony was not definitely present until the conditioned stimulus had been extended longer than one minute.

3. A differentiated stimulus of 20 sec. duration, applied after full differentiation in combination with the CS during the early synchrony response, briefly desynchronized that response, without disturbing the total duration of synchrony or the overall conditioned electrographic response pattern.

4. When combined with the CS and associated to a withholding of reinforcement, the differentiated stimulus evoked marked synchrony during the standardized activation response to the second half of the delayed conditioned stimulus.

5. Interpretations of these findings in relation to Pavlovian inhibition, hypnogenic inhibition theory of sleep, and competitive interactions in the brain are discussed.

RÉSUMÉ

1. Chez trois chats, un stimulus conditionné auditif retardé (2 min.) associé à un choc modéré à la peau a produit au cours de l'enregistrement électrographique de sommeil un tracé caractéristique de: (*a*) une activation initiale courte, suivie de (*b*) une période synchrone plus prolongée, qui se modifiait d'habitude à mi-chemin du SC à (*c*) un retour de l'activation persistant jusqu'à l'arrivée du stimulus non conditionné. Les points d'enregistrement les plus importants dans le developpement de l'activation et montrant la plus grande résistance au synchronisme étaient le cortex auditif, la formation réticulaire, et l'hippocampe. Les points qui démontraient la prédominance réciproque du synchronisme et de la résistance à l'activation étaient dans le cortex associatif.

2. Le degré et la durée du synchronisme présents au cours de la première moitié du SC variaient inversement à l'intensité de la SNC, et directement avec la progression des essais au cours d'une séance journalière donnée. Le synchronisme n'était pas présent de façon définitive tant que la durée du stimulus conditionné ne dépassait pas une minute.

3. Un stimulus différentié d'une durée de 20 sec., appliquée après une différentiation complète associée au SC au cours de la réponse synchrone précoce, désynchronisait brièvement cette réponse, sans déranger la durée totale du synchronisme ou le tableau général de la réponse électrographique conditionnée.

4. Le stimulus différentié, lorsqu'il était associé au SC et à une rétention de renforcissement, évoquait du synchronisme marqué au cours de la réponse d'activation standardisée à la deuxième moitié du stimulus conditionné retardé.

5. On discute les interprétations de ces découvertes par rapport à l'inhibition Pavlovienne, à la théorie d'inhibition hypnogène, et les interactions concurrentes du cerveau.

ZUSAMMENFASSUNG

1. Bei drei Katzen produzierte ein verzögerter (2 Min.) akustischer bedingter Reiz assoziiert mit einem mässigen elektrischen Schock, welcher kutan appliziert wurde, die folgende charakteristische Sequenz von Veränderungen im Schlafelektroenzephalogramm: (*a*) eine initiale kurze Aktivierung gefolgt von (*b*) einer etwas längeren Periode synchroner Aktivität, welche im allgemeinen in der Mitte des bedingten Reizes sich veränderte in (*c*) eine wiederkehrende Aktivierung, welche bis zur Applikation des unbedingten Reizes andauerte. Das Auftreten der Aktivierung war am ausgeprägtesten in der Hörrinde, in der Formatio reticularis und im Hippocampus, und dieselben Regionen zeigten auch die grösste Resistenz gegenüber dem Auftreten synchroner Aktivität. Im Gegensatz zu dem, zeigte die assoziative Rinde das umgekehrte Verhalten mit prädominierend synchroner Aktivität und Resistenz gegenüber Aktivierung.

2. Der Grad und die Dauer der Synchronisierung während der ersten Hälfte des bedingten Reizes waren umgekehrt proportional zur Intensität des unbedingten Reizes und direkt proportional zur Zahl der wiederholten Reizungen, welche in einer täglichen Session appliziert wurden. Synchronisierung war nur dann in klarer Weise vorhanden, wenn der bedingte Reiz über mehr als eine Minute ausgedehnt wurde.

3. Ein differenzierter Reiz von 20 Sekunden Dauer, welcher nach vollausgebildeteter Differenzierung in Kombination mit dem bedingten Reiz während der frühen synchronen Phase der Reizantwort präsentiert wurde, führte zu einer kurzen Desynchronisation der Reizantwort ohne jedoch die Gesamtdauer der Synchronisation oder den Gesamtaspekt der bedingten elektrographischen Antwort zu stören.

4. Wenn der differenzierte Reiz mit dem bedingten Reiz assoziiert wurde und die Verstärkung ausblieb, erfolgte während der standardisierten Aktivisierungsreizantwort auf die zweite Hälfte des verzögerten bedingten Reizes eine auffällige Synchronisierung der Aktivität.

5. Diese Ergebnisse und ihre Interpretation werden besprochen in Beziehung mit dem Problem der Pawlowschen Hemmung, der hypnogenen Hemmungstheorie des Schlafes und dem Wettstreit der Erregungen im Gehirn.

The authors acknowledge with pleasure the assistance of Miss Kate Gruen in histology and preparation of figures.

REFERENCES

ALEXANDER, L. Apparatus and method for the study of conditional reflexes in man. *A.M.A. Arch. Neurol. Psychiat.*, **1958**, *80*: 629-649.

BECK, E. C., DOTY, R. W. and KOOI, K. A. Electrocortical reactions associated with conditioned flexion reflexes. *EEG Clin. Neurophysiol.*, **1958**, *10*: 279-289.

BREMER, F. The neurophysiological problem of sleep. In Delafresnaye, J. F. (Ed.), *Brain Mechanisms and Consciousness, A Symposium*, Springfield, Illinois: Charles C. Thomas, **1954**, 137-157.

GASTAUT, H. The role of the reticular formation in establishing conditioned reactions, in Jasper, H. H. *et al.* (editors), *Reticular Formation of the Brain*, Boston, Little Brown and Co., **1958**.

GREEN, J. D. and ARDUINI, A. A. Hippocampal electrical activity in arousal. *J. Neurophysiol.*, **1956**, *19*: 424-437.

HESS, W. R. *Diencephalon*, New York: Grune & Stratton, **1954**.

JASPER, H. and SHAGASS, C. Conditioning the occipital alpha rhythm in man. *J. Exp. Psychol.*, **1941**, *26*: 373-388.

JASPER, H. and AJMONE-MARSAN, C. *A Stereotaxic Atlas of the Diencephalon of the Cat*, Ottawa, National Research Council of Canada, **1954**.

JOHN, E. R. Discussion in Brazier M. A. B. (Ed.); *First Conference on Central Nervous System and Behavior*, New York: Josiah Macy Jr. Foundation, **1959**.

JOUVET, M. et HERNÁNDEZ-PEÓN, R. Mécanismes neurophysiologiques concernant l'habituation, l'attention, et le conditionnement. In Fischgold, H. et Gastaut, H. (Ed.). *Conditionnement et Réactivité en Electroencéphalographie. EEG Clin. Neurophysiol.*, Suppl. No. 6, **1957**, 39-49.

KLEITMAN, N. *Sleep and Wakefulness*, Chicago, U. of Chicago Press, **1939**.

MORRELL, F. and JASPER, H. Electrographic studies of the formation of temporary connections in the brain. *EEG Clin. Neurophysiol.*, **1956**, *8*: 201-215.

MOTOKAWA, K. and HUZIMORI, B. Electroencephalograms and conditioned reflexes. *Tohoku J. Exp. Med.*, **1949**, *50*: 215-223.

PAVLOV, I. P. *Conditioned Reflexes. An Investigation of the Physiological Activity of the Cerebral Cortex*, London: Oxford University Press, **1927**.

ROWLAND, V. Differential electroencephalographic response to conditioned auditory stimuli in arousal from sleep. *EEG Clin. Neurophysiol.*, **1957**, *9*: 585-594.

ROWLAND, V. Discussion in Brazier, M. A. B. (Ed.); *First Conference on Central Nervous System and Behavior*, New York: Josiah Macy Jr. Foundation, **1959**.

RUSINOV, V. S. and RABINOVICH, M. Y. Electroencephalographic researches in the laboratories and clinics of the Soviet Union. *EEG Clin. Neurophysiol.*, Suppl. No. 8, **1958**.

YOSHII, N. and HOCKADAY, W. J. Conditioning of frequency-characteristic repetitive electroencephalographic response with intermittent photic stimulation. *EEG Clin. Neurophysiol.*, **1958**, *10*: 487-502.

Reference: GLUCK, H. and ROWLAND, V. Defensive conditioning of electrographic arousal with delayed and differentiated auditory stimuli. *EEG Clin. Neurophysiol.*, **1959**, *11*: 485-496.

PRINTED IN CANADA

THE BLOCKING OF THE ROLANDIC WICKET RHYTHM AND SOME CENTRAL CHANGES RELATED TO MOVEMENT [1, 2]

GIAN EMILIO CHATRIAN, M.D., MAGNUS C. PETERSEN, M.D. and JORGE A. LAZARTE, M.D.

Rochester State Hospital, Rochester, Minn.

(Received for publication: August 4, 1958)

Under the name of "rythme en arceau" Gastaut and co-workers (1952) and Gastaut (1952) have described in scalp, as well as in cortical, electrograms a rhythm composed of arch-shaped waves appearing in fairly regular spindles on the rolandic regions at the rate of 7 to 11 (usually 9) per second. This rhythm may occur unilaterally or bilaterally. In the latter case the spindles usually appear asynchronously on the two hemispheres. According to Gastaut and co-workers (1952) the "en arceau" rhythm is little modified by opening of the eyes or by mental calculation, but it is blocked by exteroceptive stimuli and particularly by movements either "spontaneous" (voluntary or automatic) or "provoked" (passive or reflex). This rhythm probably could be identified with the "precentral alpha rhythm" described in an early study by Jasper and Andrews (1938), with the precentral "alphoid activity" of Maddocks and associates (1951), and with the "high voltage rolandic alpha rhythm" of Schütz and Müller (1951). Other observations on this rhythm and on its reactivity have been published by Magnus (1954), Gastaut and co-workers (1954, 1957), Lelord (1957), Roger and associates (1957a, 1957b), Buser and Roger (1957), Klass and Bickford (1957) and Beek (1958). In the present study this arch-shaped rolandic rhythm is referred to as "wicket rhythm" (Gastaut and co-workers 1954).

MATERIALS AND METHODS

Analysis of the most recent 500 routine scalp recordings done in our laboratory has revealed the presence of a rolandic wicket rhythm in 18 persons. Two of them were classified as having chronic undifferentiated schizophrenic reaction; one as having paranoid schizophrenic reaction; two as having involutional psychotic reaction; three as having sociopathic personality disturbance; two as having chronic convulsive disorder; one as having acute post-traumatic brain syndrome; one as having psychotic depressive reaction. Finally, six were apparently normal relatives of patients suffering from Huntington's chorea, and thus members of a group who have undergone electroencephalographic study periodically in our laboratory as part of an investigation of this disease. The age of the above patients and subjects ranged between 14 and 72.

Used for electroencephalographic recordings were 19 scalp electrodes placed according to the 10/20 system again recommended recently by the International Federation of Societies for Electroencephalography (Jasper 1958), two reference electrodes (a neck collar and a chin electrode), and occasionally additional scalp electrodes. The tracings were obtained by means of a Grass 16-channel electroencephalographic assembly comprised of two 8-channel electroencephalographs connected to a common 16-channel ink-writing unit. The muscular discharge associated with movement was documented by surface electromyographic recordings. A four-beam Electronic Tube Corporation cathode-ray oscillograph was utilized for combined recordings of the electroencephalogram, the electromyogram, and the sounds of the investigator's voice.

[1] This study was supported in part by a research grant from the Minnesota Department of Public Welfare.

[2] An abstract of this paper has been read at the meeting of the American Electroencephalographic Society, Atlantic City, New Jersey, June 12 to 14, 1958.

Passive movements were those accomplished by the investigator's action with no apparent participation of the patient, who indeed was asked to relax as much as possible. Usually the passive movement was flexion of one hand or one arm. For reflex movements the knee jerk was provoked by a short tapping of the patellar tendon and flexion of the arm by percussion on the bicipital tendon.

In studying the effects on the wicket rhythm of voluntary movements, separate investigation was made of the movements performed spontaneously and of those performed on command. Spontaneous movements usually were obtained by instructing the patient before the recording to flex, on his own initiative during the test, the right thumb or hand, the left, or both. Movements on command were obtained usually by orders given the patient while he was awake and resting with the eyes closed — for example, "flex your right hand". In some tests the duration of the order was longer or shorter; and it was reduced in a few instances to a mere signal — for example, a flash of light.

Various degrees of the patient's attention have been obtained by means of tests graded from the simple opening of the eyes to the visual analysis of a complex pattern — for instance, one of the test pictures used in a previous study of the lambda waves in the depth of the occipital lobe (Chatrian *et al.*, to be published). This study includes observations done during drowsiness that occurred spontaneously in some tests.

RESULTS

In our series the wicket rhythm (fig. 1) was found to present considerable variation in degree of persistence, regularity, shape, voltage, and to some extent frequency. This was noted not only from one patient to another but also in the same patient from day to day, without demonstrable reasons. The "wicket" shape of the component waves was often more obvious when recorded at a paper speed of 1.5 cm. per sec. (as by the French authors) than when recorded at our usual speed of 3 cm. per sec. The voltage of the waves usually was between 20 and 80 μV. and the frequency between 7.5 and 11 c/sec. The wicket pattern was found to predominate constantly on the central electrodes in both bipolar and monopolar recordings. Ordinarily it was associated

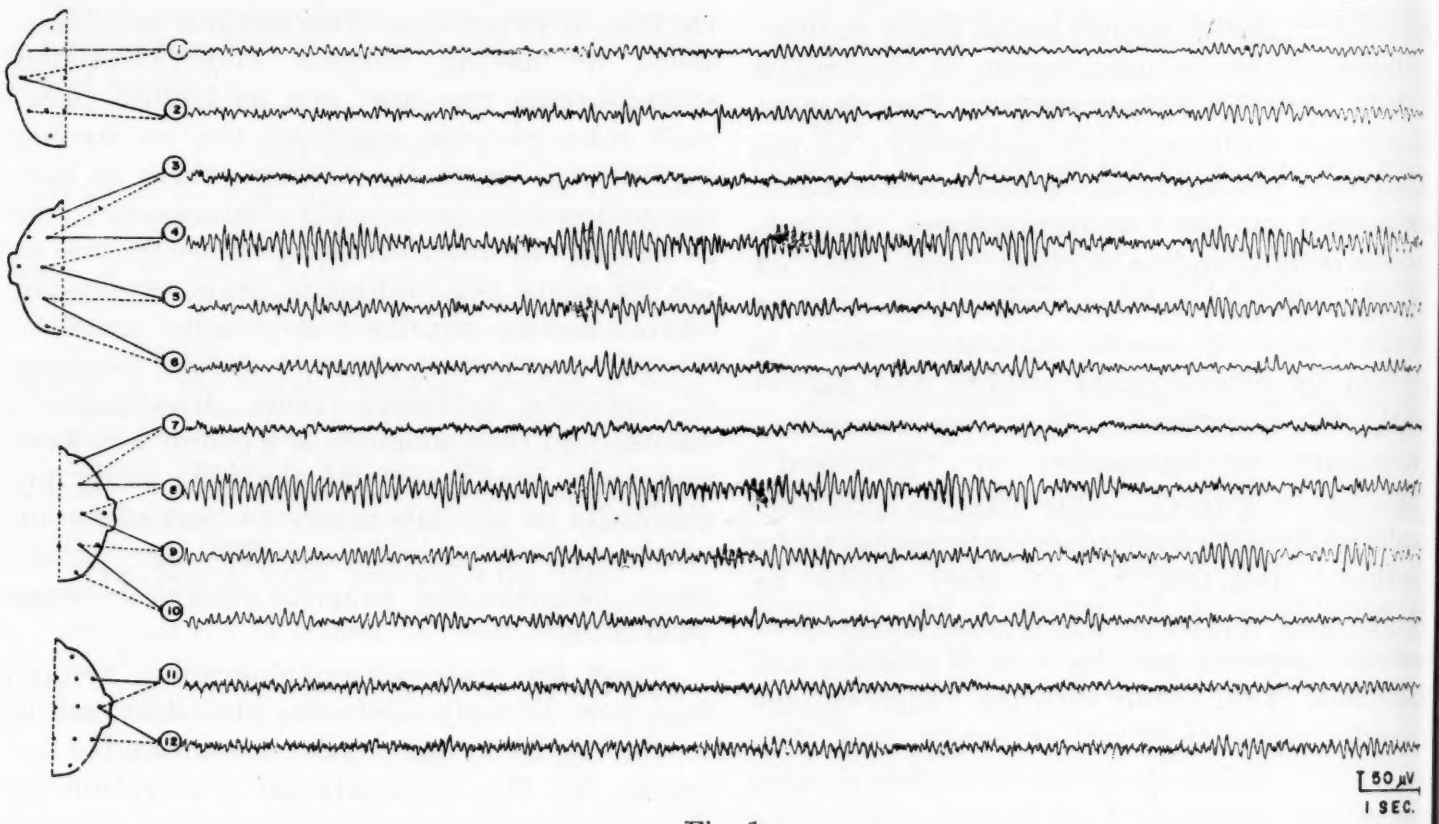


Fig. 1

Typical wicket rhythm recorded from the central areas of the scalp in a female patient 42 years old (involutional psychotic reaction).

with bursts of beta waves (15 to 25 per sec.) of lower voltage. These potentials were often, but not constantly, twice as rapid as the wicket waves. The wicket rhythm may be recorded also from the depths of the rolandic area (fig. 2, upper tracings) by means of implanted multielectrode leads (Dodge and associates 1953).

A blocking of the rolandic wicket rhythm was noted in relation with movement (fig. 3 through 8). This phenomenon consists in the disappearance of the wicket rhythm, which is replaced by potentials of 15 to 35 c/sec., of voltage not usually exceeding 10 μV. After return of the moving part of the body to the resting position, the wicket rhythm reappears and sometimes even shows some degree of rebound.

Passive Movements. Usually the passive movements (for example, flexion of one hand) are associated with blocking of the wicket rhythm (fig. 3). This phenomenon is noted on both hemispheres. It may occur at approximately the same time on both rolandic areas or 200 to 300 msec. earlier on the contralateral side than on the homolateral. The effect on the contralateral side ordinarily is the stronger. In the patient from whom the recordings which illustrate this article (except fig. 2) were taken, simultaneous oscillographic recordings of the electromyographic discharges and of the wicket rhythm of the side contralateral to the movement demonstrated a delay of 150 to 220 msec., averaging 175, between the beginning of the passive flexion of one hand and the wicket-rhythm blocking. The blocking provoked by passive movement shows convergence in the same point, no matter which of various parts of the body is moved.

After the passive movement ceases the wicket rhythm reappears, often on the contralateral hemisphere before the homolateral, as already stated with regard to voluntary movements.

If the movement is repeated many times,

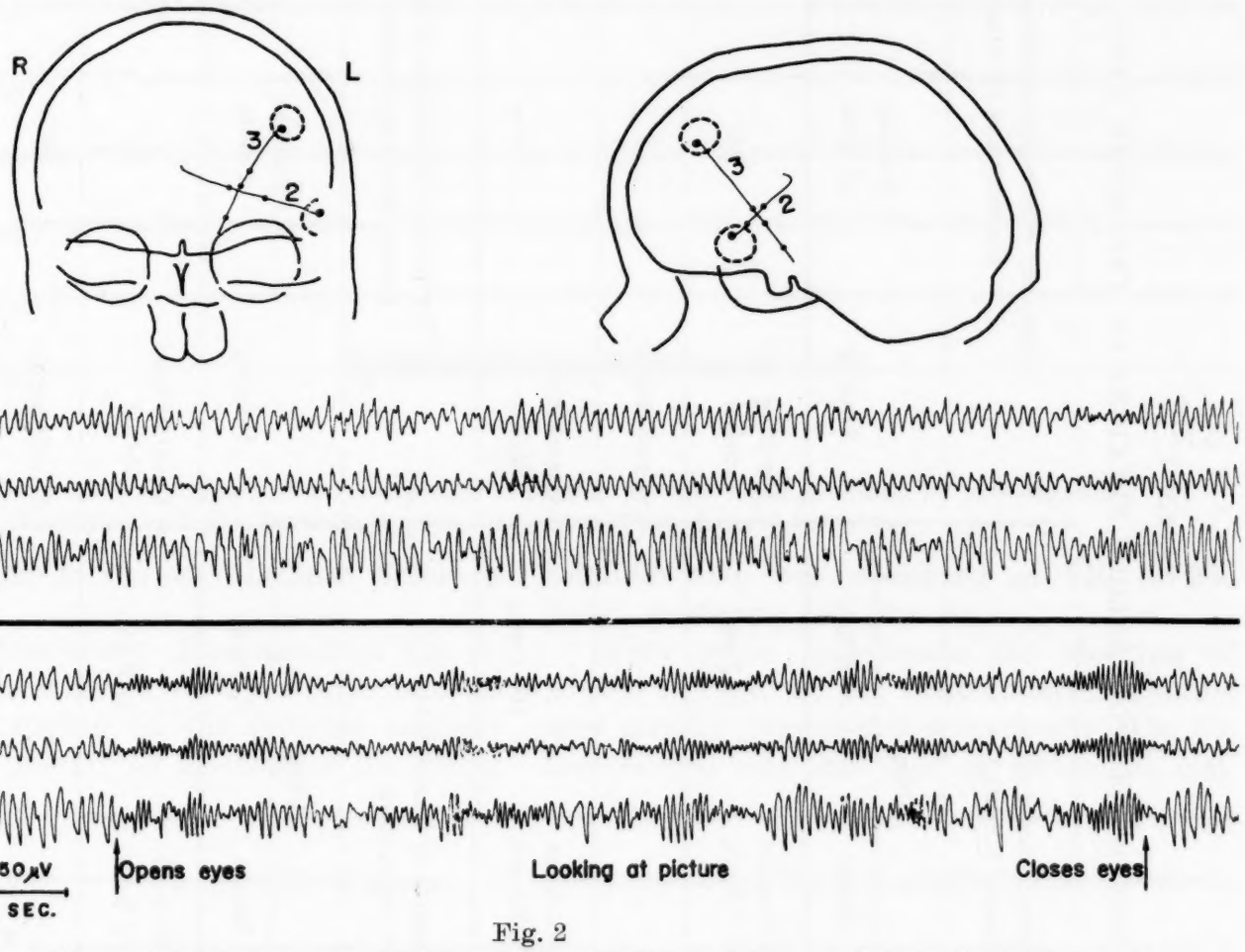


Fig. 2

Wicket rhythm recorded from the depths of the rolandic area in a female patient 35 years old (temporal lobe epilepsy). (Recording obtained in our laboratory by Dr. C. W. Sem-Jacobsen.)

TABLE I

RESULTS OF 100 SPONTANEOUS FLEXIONS OF THE RIGHT HAND

Temporal relationships between onsets of contralateral and of homolateral blocking

Finding	Number of tests	Delay	
		Range	Average
Contralateral earlier	73	100 msec. to 7.7 sec.	1.15 sec.
Simultaneous	15	—	—
Homolateral earlier	12	100 msec. to 2.4 sec.	160 msec.

Temporal relationships between onsets of homolateral blocking and of muscular contraction

Finding	Number of tests	Delay	
		Range	Average
Blocking earlier	68	50 msec. to 6 sec.	1.15 sec.
Simultaneous	19	—	—
Contraction earlier	13	100 to 350 msec.	190 sec.

Temporal relationships between onsets of contralateral blocking and of muscular contractions

Finding	Number of tests	Delay	
		Range	Average
Blocking earlier	99	50 msec. to 7.5 sec.	1.5 sec.
Simultaneous	1	—	—
Contraction earlier	—	—	—

Temporal relationships between contralateral and homolateral reappearances of wicket rhythm

Finding	Number of tests	Delay	
		Range	Average
Contralateral earlier	56	200 msec. to 2 sec.	870 msec.
Simultaneous	30	—	—
Homolateral earlier	17	100 msec. to 2 sec.	750 msec.

rhythm
noted.
Re
flex ty
by a
are fol

its ef
varia
time
the m
after

its effect usually decreases gradually after a variable number of repetitions. If at this time another part of the body is moved, or if the movement is stopped and then begun again after an interval, a blocking of the wicket rhythm (fig. 4). By means of oscillographic recordings the delay between the first abrupt electromyographic deflection indicating tapping of the patellar tendon and the beginning of the blocking effect on the contralateral

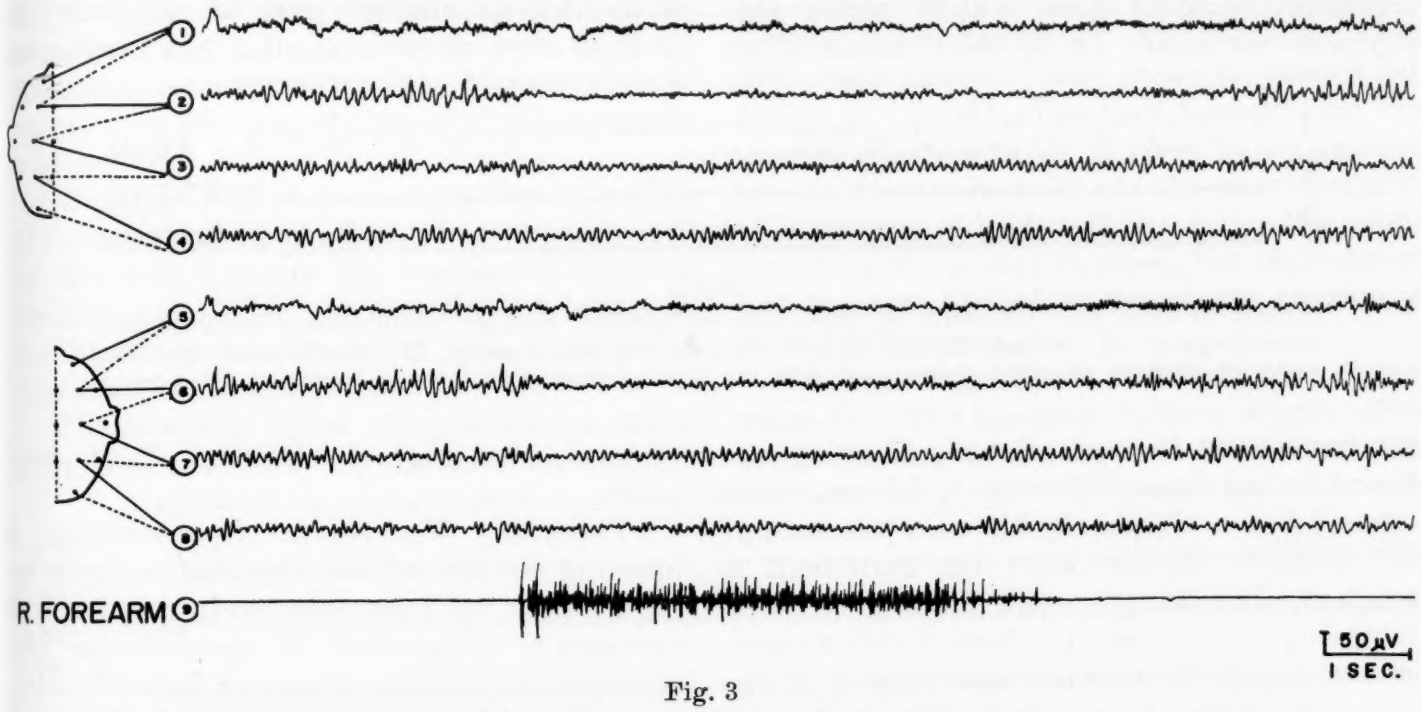


Fig. 3

Effect on wicket rhythm of both hemispheres of flexion of right hand produced by investigator's action. Electromyographic recordings from anterior surface of right forearm.

rhythm similar to the one obtained before is noted.

Reflex Movements. Movements of the reflex type (for example, the knee jerk obtained by a short tapping on the patellar tendon) are followed quickly by blocking of the wicket rolandic area was measured as 140 to 230 msec., averaging 185 (fig. 5).

With reflex movements the blocking of wicket rhythm on the contralateral rolandic area usually predominates markedly. On the homolateral side this type of movement may

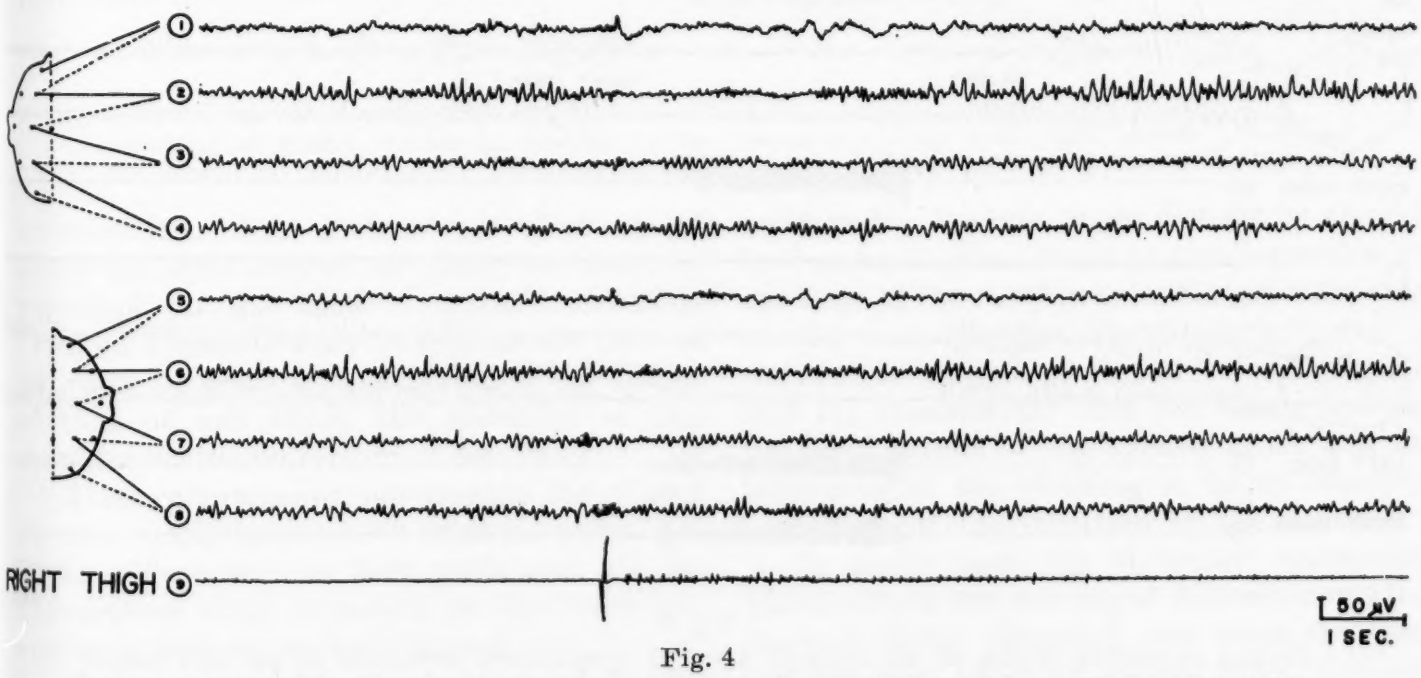


Fig. 4

Effect of knee jerk provoked by short tapping on right patellar tendon. Electromyographic recording obtained from anterior surface of thigh.

provoke a blocking of the wicket rhythm, but more often only some degree of decrease in voltage of the wicket is noted, and in other tests no changes are observed on that side.

The duration of the blocking on the contralateral rolandic area usually shows considerable variation. In 50 observations of reflex movement the contralateral blocking was found to last from 300 msec. to 6.5 sec., averaging 1.6 sec. Ordinarily the reappearance of the rolandic rhythm after the movement is gradual. The duration and the degree of bilaterality of the blocking effect of reflex movements appear to be somewhat related to the intensity of the tapping and to the consequent magnitude of the reflex movement.

If the stimulus is repeated many times, the rolandic effect of the movement usually declines rapidly. If at this time the stimulus is applied to another part of the body, or if it is stopped, then applied again after an interval, the original blocking effect reappears.

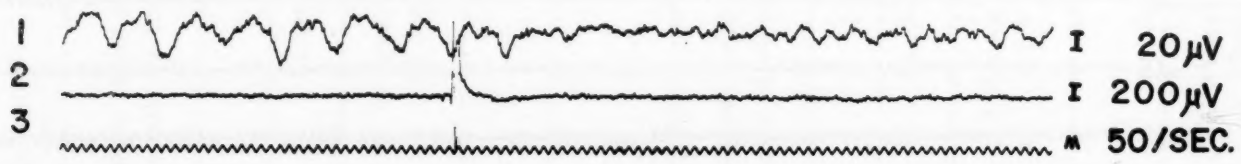


Fig. 5

Effect of knee jerk provoked by percussion of patellar tendon: simultaneous oscillographic recordings of (1) wicket rhythm of left rolandic region of scalp, (2) electromyogram from anterior surface of right thigh, and (3) the time-marker signal (sine waves at 50 c/sec.).

Voluntary Movements. Spontaneous. A blocking of the wicket rhythm on both rolandic areas has been observed in relation with movements designated as spontaneous (for example, the flexion of one or both thumbs).

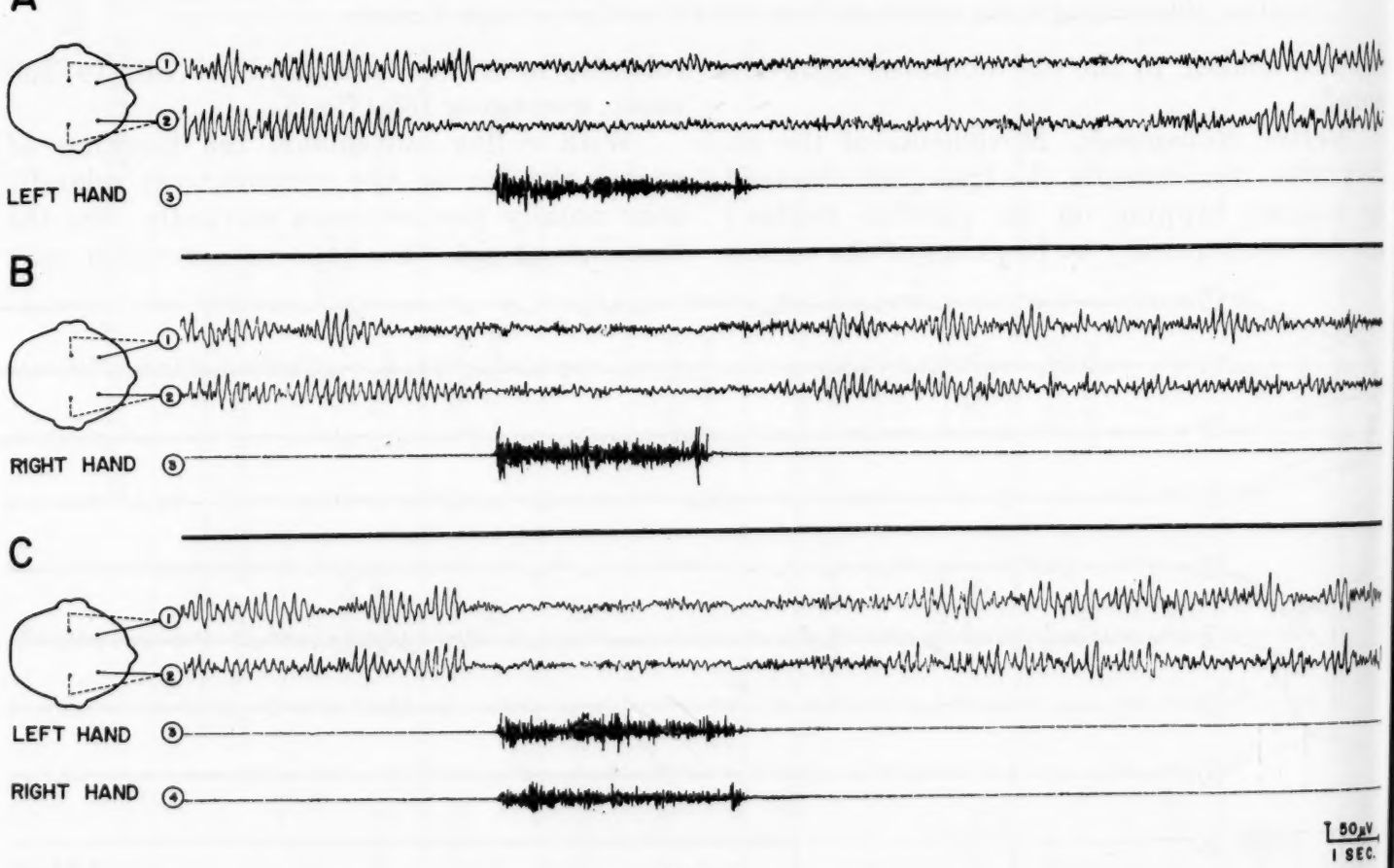


Fig. 6

Effects on wicket rhythm of the rolandic areas of spontaneous movement of the left thumb (section A), of the right thumb (section B) and of both thumbs (section C). Electromyographic recording from surfaces of thenar eminences.

When one thumb is moved (fig. 6A and B) the blocking effect usually is noted on the contralateral rolandic area earlier than on the homolateral. In the majority of the tests of simultaneous flexion of both thumbs (fig. 6C) the blocking involves the two rolandic areas simultaneously. In unilateral and bilateral spontaneous movements alike, the wicket blocking usually precedes the onset of the muscular contraction.

With unilateral movements the blocking of the wicket rhythm often is more pronounced on the side opposite the movement than on the same side. When the movement is bilateral, the blocking usually is of about the same degree on both hemispheres.

The blocking effect of spontaneous movement does not show any definite somatotopic organization. For instance, a blocking of about the same degree and duration could be provoked on the same "central" electrode (located approximately in the middle part of the rolandic area) by the flexion of one finger or that of one hand, the elevation of one shoulder, or the movement of one foot.

After spontaneous movements the wicket rhythm reappears on both rolandic areas, but if the movement has been unilateral the reappearance often is earlier on the contralateral area than on the homolateral.

The patient from whom most of the illustrations of this article were taken performed, in the course of the same recording, 100 spontaneous movements of flexion of the right hand. The results of these tests are reported in the table.

Following Command. A blocking effect has been noted in relation to the investigator's command for movement (for example, "flex your right thumb") and to the movement following it (fig. 7). The first time or first few times the spoken order is given to the patient, the blocking ordinarily has the characteristics of a generalized arousal involving the alpha as well as the wicket rhythm; but then the effect becomes limited to the wicket rhythm of the rolandic areas.

In recordings from the first tests it appears that the blocking follows shortly after the beginning of the spoken order, and this relationship becomes more distinct in the following tests. Simultaneous oscillographic recordings of the rhythm from the rolandic area, of the electromyographic discharges, and of the sounds of the investigator's voice (fig. 8A and B) demonstrate that the delay between the first sounds of the spoken order and the beginning of the blocking is fairly constant, regardless of the duration of the order.

In early tests the muscular contraction which effects the movement follows soon after the end of the command, but when the same test has been repeated several times, the contraction often is seen to begin simultaneously

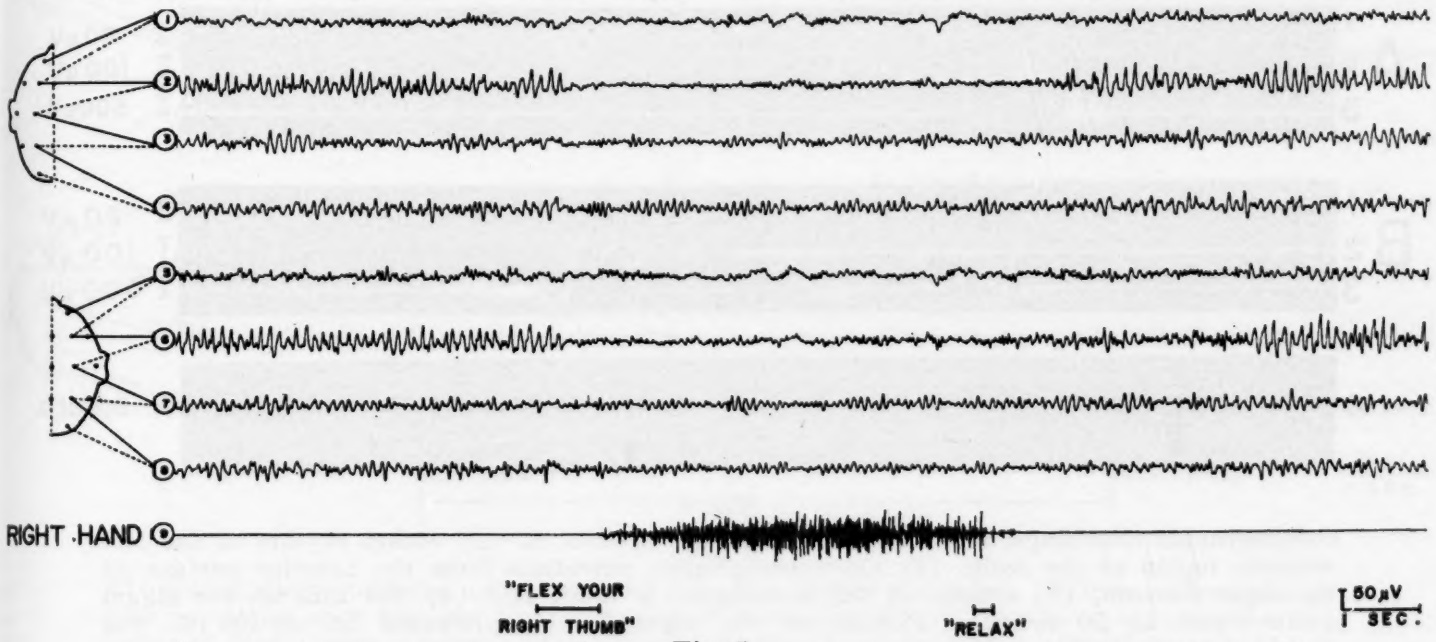


Fig. 7

Blocking of wicket rhythm in relation to the command, "Flex your right thumb", and to the movement following it. Electromyographic recording from surface of thenar eminence.

with, then gradually before, the end of command.

In 12 tests of the patient from whom the recordings that illustrate this article (except fig. 2) were taken, the interval from start of command to start of blocking ranged from 230 to 410 msec., averaging 350. The electromyographic discharge appeared at approximately the same time as or shortly after the blocking (fig. 8A), or at a considerable interval after it (fig. 8B), depending on the duration of the command. In fact, prolonging the duration of the spoken order may delay considerably the beginning of the muscular contraction without affecting the time interval between the beginning of the spoken order and the onset of the blocking effect. Some degree of anticipation of the motor response with repetition of the order is seen in figure 8B.

The blocking of the wicket rhythm before the movement begins is noted simultaneously on both hemispheres (fig. 7). Usually it is approximately symmetrical and does not show any definite somatotopic organization. Then during the muscular contraction the blocking effect usually predominates on the hemisphere contralateral to the movement.

If the muscular contraction is maintained for long (more than 1 min.), the wicket rhythm may gradually reappear. But if the movement is repeated many times without pause, the blocking phenomenon usually persists until the movement ceases.

Between the command instructing the patient to relax and the cessation of his muscular contraction is a delay of fairly constant length. For example, in the patient from whom the illustrations of this article (except figure 2) were obtained, the electromyographic discharge ended 700 to 800 msec. after the end of the investigator's command, "relax". Then, after a variable delay, the wicket rhythm reappears on both rolandic areas — often earlier on the contralateral hemisphere than on the homolateral. Some degree of rebound may be noted.

In certain observations the patient was asked to think, on presentation of a given signal (for example, a flash of light), of making a given movement (for example, flexion of the right arm), and, on repetition of the signal, of returning to the resting position. Under these conditions a blocking of the wicket rhythm was observed. It was noticed, however, that even in the absence of any visible movement, the electromyographic tracings from the surface of the muscles involved in the imagined movement showed some degree of muscular discharge after the onset of the blocking phenomenon. In some other tests the patient was told, "get ready to move"; and this command also was sufficient to provoke bilateral blocking.

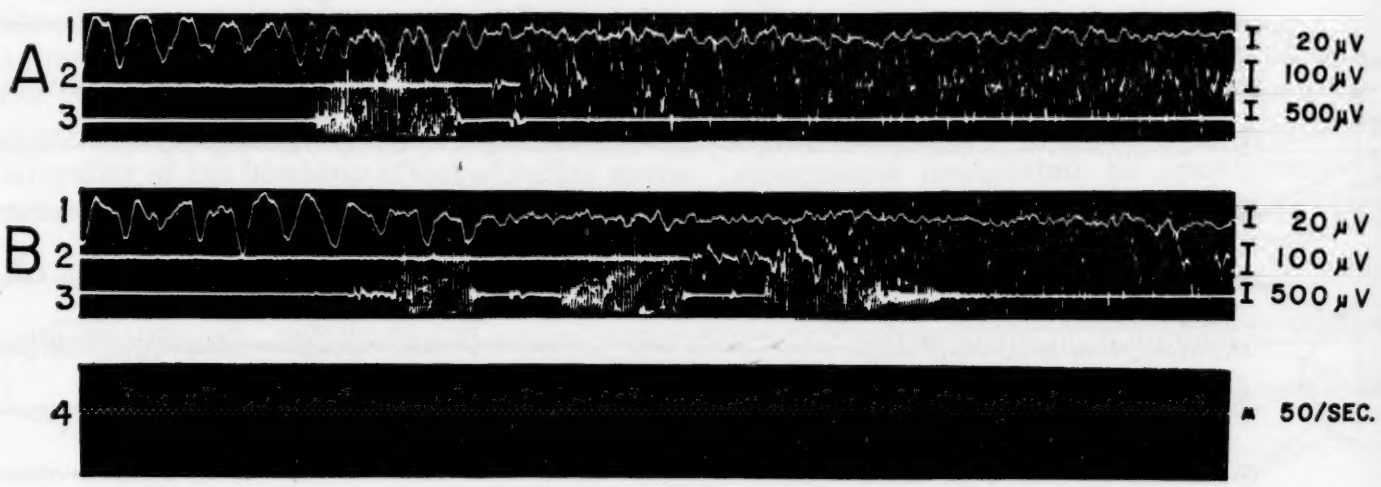


Fig. 8

Oscillographic recordings, simultaneous within each section, of (1) wicket rhythm of the left rolandic region of the scalp, (2) electromyographic potentials from the anterior surface of the right forearm, (3) sounds of the investigator's voice, and (4) the time-marker signal (sine waves at 50 c/sec.). Flexion of the right hand represented in section A was provoked by the order, "Right"; in section B by the order, "Flex right hand".

Effects of Tactile and Other Stimuli. Tactile stimuli — for instance, the slight prolonged touch of the palmar surface of one hand — were found capable of provoking a blocking of the wicket rhythm. In these tests the blocking occurs bilaterally but is stronger on the hemisphere contralateral to the stimulus. Also convergence in the same point was observed for stimulations of various parts of the body. The reappearance of the rhythm usually is noted on the contralateral side earlier than on the homolateral. Generally the wicket rhythm is modified but slightly or not at all. At the same time the blocking of the alpha rhythm is often incomplete (fig. 9, upper tracings). In some other observations, particularly when the patient is asked to fix his eyes on a given point (for example, a colored dot on a white background) the blocking of the alpha rhythm is associated with a marked decrease in amplitude of the wicket rhythm. When the patient is required to look actively at a bright, complex, test picture a complete blocking of the wicket rhythm may

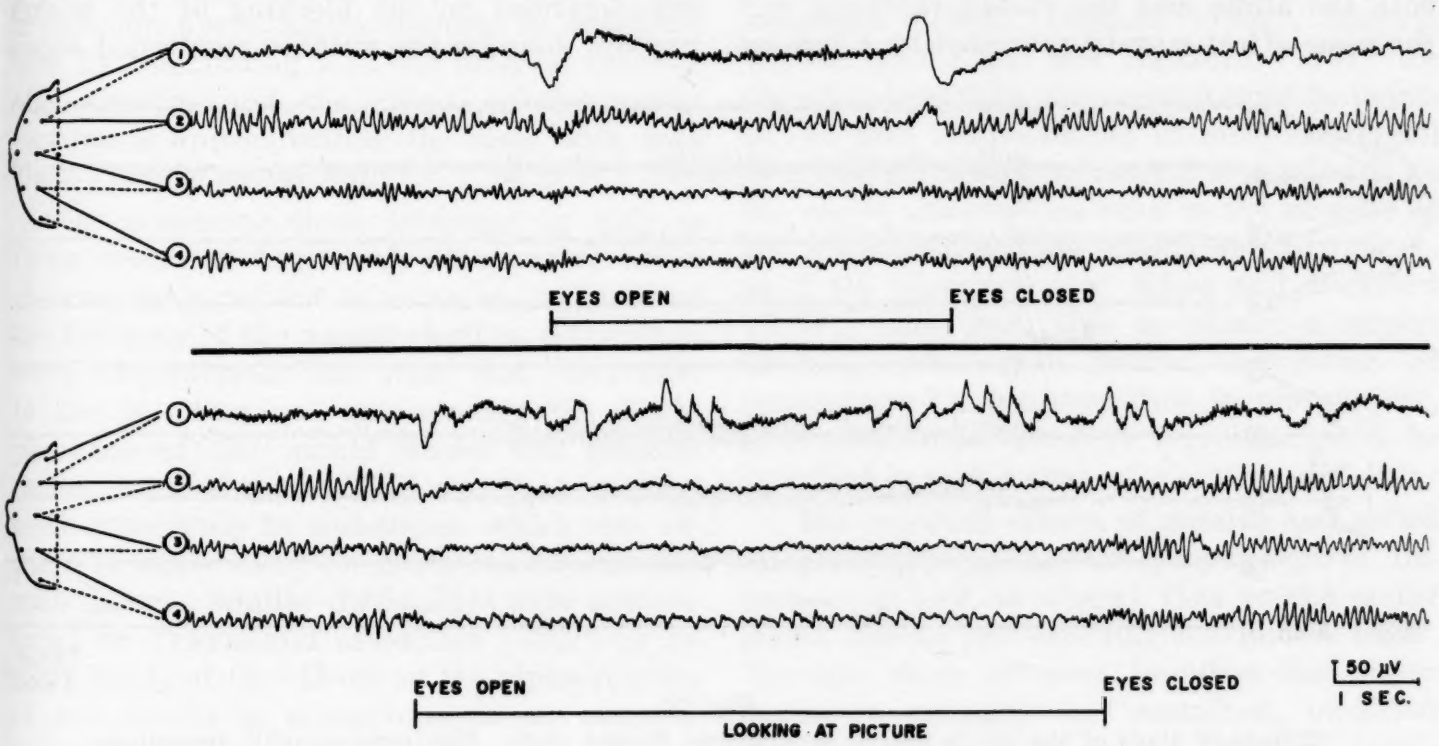


Fig. 9

Effects of simple opening and closing of the eyes (upper tracings). Effects of compliance with request to open eyes and look at details of a complex colored picture representing various dishes of food (lower tracings). The picture was brightly lighted by a photoflood bulb placed behind and above the patient.

effect of tactile stimuli is less constant than effects provoked by movements.

Visual stimuli (for example, a flash of light or a burst of flashes) and auditory stimuli (for example, a click or a train of clicks of moderate intensity) did not provoke any constant significant changes of the wicket rhythm during wakefulness.

Influences of Attention and Drowsiness. Factors that usually provoke blocking of the alpha rhythm were found to provoke various degrees of effect or sometimes none on the wicket rhythm, in accord with the level of attention required. In fact, it has been noted that during the simple opening of the eyes the be noted with the alpha blocking, while lambda waves appear on the posterior regions (fig. 9, lower tracings). Also, a diffuse electroencephalographic blocking which involved to some extent the wicket rhythm has been obtained when the patient opened his eyes in complete darkness, or when his vision was blurred with a pair of glasses with a + 10 lens on each side, and even when the patient tried to visualize, with the eyes closed, the details of a test picture observed before. At times — and particularly with the eyes closed — auditory attention may be as effective as the visual. Various modes of mental activity (for example, calculating) have been seen to provoke

some degree of blocking of the wicket rhythm as well as of the alpha. In a patient from whom a wicket rhythm at 8 to 8.5 c/sec. was recorded from the depths of the rolandic area, visual and mental activity provoked disappearance of the wicket, which was replaced by bursts at 16 and sometimes at 12 per sec. (fig. 2, lower tracings).

During spontaneous drowsiness (fig. 10), both wicket and alpha rhythms disappear. At this time a sudden stimulus such as a clap of the hands may produce the reappearance of both the alpha and the wicket rhythms, and the same effect may be provoked by a passive movement. Thus during drowsiness one may observe the apparently paradoxical phenomenon of a movement bringing on the wicket rhythm.

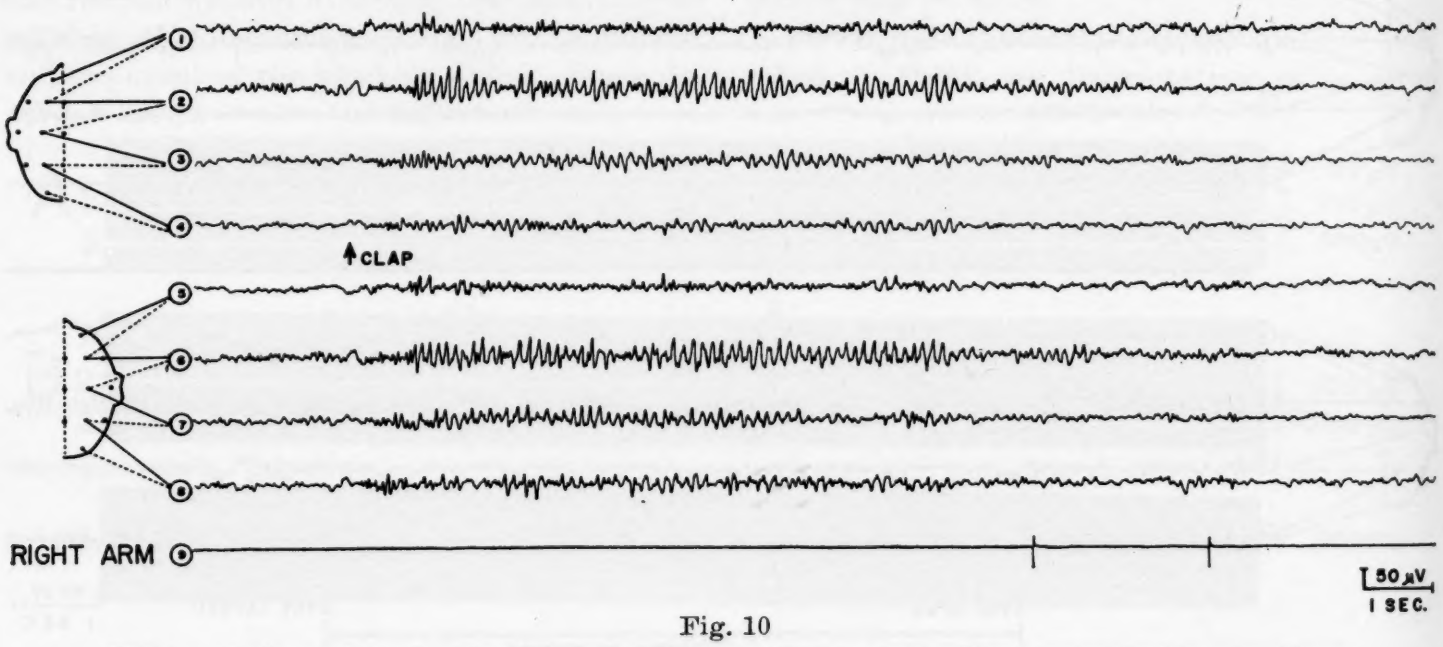


Fig. 10

Effects of claps of the hands during spontaneous drowsy state. Electromyographic recordings from anterior surface of right arm.

COMMENT

According to Gastaut and co-workers (1952, 1954) and Gastaut (1952) the wicket rhythm is the result of exaggeration with halving of the physiologic beta rhythm; and the same authors have found a positive correlation between the presence of the wicket rhythm and a large group of psychosomatic symptoms and diseases. Though our work is not primarily concerned with the clinical significance of the wicket rhythm and does not have an impressive statistical basis, we would point out that one third of the subjects in our series presenting rolandic wicket rhythms were apparently normal persons. As for the nature of the rhythm, the relationships between the frequency of the wicket rhythm and the frequency of the beta activity are not always simple. Further, the beta rhythm often is found over a wider topography than is the wicket (Magnus 1954). Close functional relationships seem to exist between those two rhythms, however, on the evidence of a common reactivity to movement and sensory stimulation. This evidence has resulted from the investigations on the blocking of the wicket rhythm done by the authors mentioned above and by us, as well as from the observations made on the beta activity of the motor regions of animals by Gay and Gellhorn (1949) and Kruger and Henry (1956, 1957) and from studies in man by Jasper and Andrews (1938), Jasper and Penfield (1949), Delgado and Hamlin (1956) and Sem-Jacobsen and associates (1956).

It should be admitted that although the blocking of an electrical rhythm is often interpreted as an "activation pattern", its intimate nature is incompletely known at the present time. Indeed, recent single-unit recordings of Ricci and co-workers (1957) demonstrate that under certain conditions many cortical cells are unaffected, and that about as many are inhibited as activated when a surface rhythm is blocked. However, figure

2 (lower tracings) shows a distinct acceleration of the rhythmic activity recorded from the depths of the rolandic region of a human patient during blocking of the wicket rhythm.

The blocking of wicket rhythm after passive as well as reflex movements, already noted by Gastaut and associates (1952) and Gastaut (1952), appears to be related to the arrival in the rolandic area of proprioceptive impulses originated by the movement. That the cortical effect of reflex movement as well as of passive movement may be produced through a common operating mechanism is suggested also by the finding that the interval between the stimulus and the effect on the wicket rhythm is approximately the same with both these types of movement.

In measuring those latencies as well as those from the beginning of a verbal order instructing a patient to move to the onset of the blocking of the wicket rhythm, difficulties were encountered that were due essentially to the fact that not uncommonly the disappearance of the wicket waves was gradual rather than abrupt. This may have caused some inaccuracy in measuring, which may explain to some extent the excessive variation of such delays. Similar difficulties were encountered by Travis and associates (1937) in an early study of the effects on the alpha rhythm of movements as a response to an external stimulus.

It must be pointed out that the predominance of the proprioceptive projections in the so-called motor area, demonstrated in man by Gastaut (1952) and in animals by Gay and Gellhorn (1949) and Kruger and Henry (1956, 1957), as well as the bilaterality of the response already noted by Gastaut (1952) and associates (1952), and the convergence in the same point of the rolandic area for the effects of passive and reflex movements of various parts of the body (so far as can be determined by scalp recordings) are in contradiction with the doctrines of classic physiology. Analogous speculation may be applied to the effect on the wicket rhythm of tactile stimuli, which was observed also by Gastaut and associates (1952) and Gastaut (1952) and by Magnus (1954).

The usual occurrence of the blocking of the wicket rhythm before the start of the spontaneous movement (which is at variance with the findings of Kruger and Henry 1956, 1957) suggests that proprioceptive afferences are not likely to play an important role in the initiation of the blocking phenomenon. A further evidence supporting this assumption is that a blocking effect may be provoked also by suggested mental representation of a movement or by readiness to move, as already described by Jasper and Penfield (1949) in regard to the beta rhythm, and by Gastaut and associates (1952), Gastaut (1952), Magnus (1954), and Klass and Bickford (1957) for the wicket rhythm. However, it must be pointed out that the possibility of some subliminal proprioceptive inflow cannot be excluded in the above observations even in the absence of any electromyographic discharge. In this regard the observation of Klass and Bickford (1957), who were able to obtain a wicket blocking even upon mental instigation of movement of a phantom limb in one patient, is crucial, since afferent impulses could be excluded in such a case.

The reported effects of passive and reflex movements suggest that proprioceptive impulses (as well as others) flow to the motor cortex during the muscular contraction itself. Through these afferent impulses the motor discharge probably is "sustained, modified and directed into the proper pattern" (Gellhorn 1953), according to the classic work of Sherrington (1933) and to the more recent investigations of Hyde and Gellhorn (1949). This mechanism may be regarded therefore as having the properties of a feed-back system (Gastaut 1952).

The predominantly contralateral projection of proprioceptive afferences reported above may explain to some extent the predominance of the wicket blocking on the contralateral hemisphere during movements performed on command. The observation that the blocking of the wicket rhythm usually precedes the start of such a movement is at variance with the findings of Gastaut and associates (1952) but confirms the results of later work by Gastaut alone (1952) and of some observations by Klass and Bickford (1957). Probably this phenomenon may be

interpreted as a conditioned electrocortical reaction preceding the motor reaction to the verbal order acquired during ontogenetic development (Ivanov-Smolenski 1952).

The contralateral blocking of wicket rhythm preceding spontaneous movement suggests that while the patient is planning a given movement, a stream of impulses flows from some cortical or subcortical positions to the motor cortex of the opposite hemisphere, the blocking of the wicket rhythm being thus caused. This may have the effect of preparing the precentral area for action, probably by increasing its susceptibility to more elaborate volitional messages resulting from complex integrations, which supply to the motor neurons the plan of movement in the form of spatially and temporally varied patterns of impulses (Penfield 1954). The lack of a definite somatotopic organization of the contralateral wicket blocking (so far as can be determined in scalp recordings) and of the later homolateral blocking may indicate the marshalling of synergistic actions of muscular groups on the side contralateral to the movement, as well as on the homolateral side.

That after movement the wicket rhythm reappears on the contralateral hemisphere earlier than on the homolateral suggests that the cessation of the afferent bombardment associated with the movement influences the contralateral rolandic area more promptly and directly than the homolateral.

The observed effects on the wicket rhythm of attention and mental activity are at variance with the reports of Gastaut and associates (1952), Gastaut (1952), and Klass and Bickford (1957). Selective blocking of the occipital alpha rhythm occurs with visual stimulations of moderate intensity (Jasper and Andrews 1938). Contrariwise, selective blocking of the wicket can be produced by movement and by tactile stimulations of moderate intensity. This observation suggests the functional independence of the two rhythms in such stimulating situations. Stimulations of greater intensity — particularly those requiring considerable concentration of attention — are capable of provoking a generalized response involving both the alpha and the wicket rhythms. The latter finding, together with that of the effects of drowsiness and of sensorial stimuli during the drowsy state, suggests that the wicket rhythm is also, to some extent, under the control of the mechanisms which are responsible for the regulation of the state of consciousness.

SUMMARY

Analysis of the 500 most recent scalp recordings made in the electroencephalographic laboratory at the Rochester (Minnesota) State Hospital has revealed the presence of a rolandic wicket (''en arceau'') rhythm in 18 persons.

Passive movements and reflex movements provoked blocking of the wicket rhythm. The interval between the beginning of the movement and the blocking was approximately the same for both types of movement. In comparison with the effect of passive movement, the blocking provoked by reflex movement was shorter and predominated more markedly on the contralateral hemisphere.

Blocking of the wicket rhythm was noted also in relation to spontaneous voluntary movements. When these were unilateral the blocking effect involved both central areas, usually the contralateral before the homolateral. The beginning of the contralateral blocking usually preceded the onset of the muscular contraction.

Blocking was observed also with movements on command. At first it had the characteristics of a generalized arousal; in succeeding tests it became limited to the wicket rhythm of the rolandic areas. The wicket blocking followed with a fairly constant short delay after the beginning of the spoken order and, depending on the duration of the order, was seen approximately simultaneously with or a varied time before the onset of the muscular contraction.

Tactile stimuli also produced bilateral blocking of wicket rhythm, with the stronger effect on the contralateral side.

Visual and mental activity were able to provoke some degree of wicket together with alpha blocking in accord with the level of attention required.

The mechanisms through which the above stimuli provoke the blocking of the wicket rhythm are discussed.

RÉSUMÉ

L'analyse des 500 derniers tracés enregistrés au Laboratoire d'Electro-encéphalographie du Rochester State Hospital (Minnesota) a démontré la présence d'un rythme en arceau rolandique chez 18 sujets. Ce rythme en arceau était bloqué par les mouvements passifs et les mouvements réflexes. L'intervalle entre le début du mouvement et le blocage était à peu près identique pour ces deux types de mouvement. Néanmoins le blocage du rythme en arceau provoqué par les mouvements réflexes était de plus courte durée que celui produit par les mouvements passifs et prédominait plus nettement sur l'hémisphère contralatéral. Un blocage du rythme en arceau a été observé aussi en relation avec les mouvements volontaires spontanés. Quand ceux-ci étaient unilatéraux le blocage intéressait les deux aires centrales mais d'habitude apparaissait plus tôt du côté hétérolatéral que du côté homolatéral. En plus, le début du blocage hétérolatéral précédait le début de la contraction musculaire.

Un blocage du rythme en arceau a été également observé lors de mouvements exécutés sur commande. Au début ce blocage avait les caractéristiques d'une réaction d'éveil généralisée mais dans les tests suivants, le blocage devenait limité au rythme en arceau des régions rolandiques. L'effet de blocage faisait suite au début de l'ordre verbal après un délai assez constant et de courte durée. Il s'installait à peu près simultanément avec la contraction musculaire ou avant celle-ci en un temps varié selon la longueur de l'ordre donné.

Des stimuli tactiles produisent également un blocage bilatéral du rythme en arceau. Cet effet est plus marqué du côté hétérolatéral.

L'activité visuelle et mentale peut provoquer un certain degré de blocage du rythme en arceau et du rythme alpha en rapport avec le niveau d'attention exigé.

Les mécanismes par lesquels les stimuli cités plus haut causent un blocage du rythme en arceau sont discutés.

ZUSAMMENFASSUNG

Eine Untersuchung der letzten 500 EEG's, welche im Rochester State Hospital (Minnesota) aufgenommen wurden, ergab, dass der "Bogenrhythmus", ("rhythme en arceau") bei 18 Personen nachgewiesen werden konnte.

Passive Bewegungen und Reflexbewegungen blockierten diesen "Bogenrhythmus". Das Interval zwischen dem Anfang der Bewegung und der Blockierung des Rhythmus war ungefähr derselbe für beide Arten von Bewegungen. Die Blockierung durch eine Reflexbewegung war jedoch kürzer als die bei einer passiven Bewegung produzierte und war in der kontralateralen Hemisphäre deutlicher zu sehen.

Blockierung des "Bogenrhythmus" wurde auch beobachtet wenn spontane Willkürbewegungen ausgeführt wurden. Wenn diese einseitig waren, so erfolgte die Blockierung in beiden Zentralregionen, im allgemeinen auf der kontralateralen Seite früher als auf der homolateralen. Der Beginn der kontralateralen Blockierung ging im allgemeinen dem Einsetzen der Muskelkontraktion voraus. Blockierung wurde auch beobachtet bei Bewegungen, welche auf Kommando ausgeführt wurden. Zuerst zeigte diese EEG-Reaktion den Charakter eines generalisierten Weckeffektes. Im nachfolgenden Test jedoch wurde die Antwort lokalisierter und beschränkte sich auf den "Bogenrhythmus" in der Zentralregion. Die Blockierung des Rhythmus erfolgte mit einer ziemlich konstanten kurzen Latenzdauer auf das gesprochene Kommando und je nachdem wie lang dieses gesprochene Kommando war, wurde entweder zur gleichen Zeit oder irgendwann vor dem Einsetzen der Muskelkontraktion beobachtet.

Berührungsreizè produzierten ebenfalls eine bilaterale Blockierung des "Bogenrhythmus", wobei die Blockierung auf der kontralateralen Seite stärker ausgeprägt war.

Visuelle und psychische Aktivität waren auch imstande, den "Bogenrhythmus" bis zu einem gewissen Grad zu blockieren, und dies ereignete sich zusammen mit Blockierung des Alpha-Rhythmus. Der Grad der Blockierung hing vom Grad der nötigen Aufmerksamkeitsspannung ab.

Die Mechanismen, mit deren Hilfe die erwähnten Reize die Blockierung des "Bogenrhythmus" bewerkstelligen, werden besprochen.

We should like to express our gratitude to Dr. H. W. Woltman, Rochester, Minnesota, to Dr. C. Ajmone-Marsan, National Institute of Neurological Diseases and Blindness, Bethesda, Maryland and to Dr. C. Henry, Institute of Living, Hartford, Connecticut for their advice and criticism. We also express appreciation to Miss Mary A. Bushey and Miss Nancy L. Moehnke, Rochester State Hospital, for their assistance and interest.

REFERENCES

BEEK, H. Age and the central rhythm ''en arceau''. *EEG Clin. Neurophysiol.*, **1958**, *10*: 356.

BUSER, P. et ROGER, A. Interprétation du conditionnement sur la base des données électroencéphalographiques. Premier Congrès International des Sciences Neurologiques. IVe Congrès International d'Electro-encéphalographie et de Neurophysiologie Clinique. VIIIe Réunion de la Ligue Internationale contre l'Epilepsie. Réunions plénières. Rapports, Discussions et Documentation. *Acta Med. Bel.*, Bruxelles, **1957**, pp. 417-444.

CHATRIAN, G. E., BICKFORD, R. G., PETERSEN, M. C., DODGE, H. W., JR., LAZARTE, J. A. and HOLMAN, C. B. A study of lambda waves with depth electrodes in humans. Read at the Conference on Electrical Studies on the Unanesthetized Brain, Georgetown University Medical School, Washington, D.C., June 10-13, **1957**. (To be published.)

DELGADO, J. M. R. and HAMLIN, H. Surface and depth electrography of the frontal lobes in conscious patients. *EEG Clin. Neurophysiol.*, **1956**, *8*: 371-384.

DODGE, H. W., JR., HOLMAN, C. B., SEM-JACOBSEN, C. W., BICKFORD, R. G. and PETERSEN, M. C. Technic of depth electrography. *Proc. Staff Meet., Mayo Clin.*, **1953**, *28*: 147-155.

GASTAUT, H. Etude électrocorticographique de la réactivité des rythmes rolandiques. *Rev. neurol.*, **1952**, *87*: 176-182.

GASTAUT, H., DONGIER, M. and COURTOIS, G. On the significance of ''wicket rhythms'' (''rythmes en arceau'') in psychosomatic medicine. *EEG Clin. Neurophysiol.*, **1954**, *6*: 687.

GASTAUT, H., JUS, A., JUS, C., MORREL, F., VAN LEEUWEN, W. S., DONGIER, S., NAQUET, R., REGIS, H., ROGER, A., BEKKERING, D., KAMP, A. et WERRE, J. Etude topographique des réactions électroencéphalographiques conditionnées chez l'homme (essai d'interprétation neurophysiologique). *EEG Clin. Neurophysiol.*, **1957**, *9*: 1-34.

GASTAUT, H., TERZIAN, H. et GASTAUT, Y. Etude d'une activité électroencéphalographique méconnue: ''Le rythme rolandique en arceau''. *Marseille méd.*, **1952**, *89*: 296-310.

GAY, J. R. and GELLHORN, E. Cortical projection of proprioception in the cat and monkey. *Proc. Soc. Exper. Biol. Med.*, **1949**, *70*: 711-718.

GELLHORN, E. *Physiological Foundations of Neurology and Psychiatry.* University of Minnesota Press, Minneapolis, **1953**, 556 pp.

HYDE, J. and GELLHORN, E. Influence of deafferentation on stimulation of motor cortex. *Amer. J. Physiol.*, **1949**, *156*: 311-316.

IVANOV-SMOLENSKI, A. G. Quoted by Buser, P. and Roger, A.

JASPER, H. H. The ten twenty electrode system of the International Federation. *EEG Clin. Neurophysiol.*, **1958**, *10*: 371-375.

JASPER, H. H. and ANDREWS, H. L. Electro-encephalography. III. Normal differentiation of occipital and precentral regions in man. *Arch. Neurol. Psychiat.*, Chicago, **1938**, *39*: 96-115.

JASPER, H. and PENFIELD, W. Electrocorticograms in man: Effect of voluntary movement upon the electrical activity of the precentral gyrus. *Arch. Psychiat.*, **1949**, *183*: 163-173.

KLASS, D. W. and BICKFORD, R. G. Observations on the rolandic arceau rhythm. *EEG Clin. Neurophysiol.*, **1957**, *9*: 570.

KRUGER, L. and HENRY, C. Observations on the electrical activity of rolandic cortex in monkey. *EEG Clin. Neurophysiol.*, **1956**, *8*: 157-158.

KRUGER, L. and HENRY, C. Electrical activity of rolandic region in the unanesthetized monkey. *Neurology*, **1957**, *7*: 490-495.

LELORD, G. Different modalities of reaction of the central and anterior rhythms at 10 c/sec. *EEG Clin. Neurophysiol.*, **1957**, *9*: 561.

MADDOCKS, J. A., HODGE, R. S. and REX, J. Observations on the occurrence of precentral activity at alpha frequencies. *EEG Clin. Neurophysiol.*, **1951**, *3*: 370.

MAGNUS, O. The central alpha-rhythm (''rythme en arceaux''). *EEG Clin. Neurophysiol.*, **1954**, *6*: 349-350.

PENFIELD, W. Mechanisms of voluntary movement. *Brain*, **1954**, *77*: 1-17.

RICCI, G., DOANE, B. and JASPER, H. Microelectrode studies of conditioning: Technique and preliminary results. Premier Congrès International des Sciences Neurologiques. IVe Congrès International d'Electro-encéphalographie et de Neurophysiologie Clinique. VIIIe Réunion de la Ligue Internationale contre l'Epilepsie. Réunions plénières. Rapports, Discussions et Documentation. *Acta Med. Bel.*, Bruxelles, **1957**, pp. 401-415.

ROGER, A., SOKOLOV, E. N. and VORONIN, L. G. The motor conditioning during wakefulness and during sleep: Electrographic study in normal man. *EEG Clin. Neurophysiol.*, **1957**a, *9*: 561-562.

ROGER, A., SOKOLOV, E. N. et VORONIN, L. G. Le conditionnement moteur à l'état de veille et pendant le sommeil: Etude électroencéphalographique chez l'homme normal. *Rev. neurol.*, **1957**b, *96*: 460-469.

SEM-JACOBSEN, C. W., PETERSEN, M. C., DODGE, H. W., JR., LAZARTE, J. A. and HOLMAN, C. B. Electroencephalographic rhythms from the depths of the parietal, occipital and temporal lobes in man. *EEG Clin. Neurophysiol.*, **1956**, *8*: 263-278.

SCHÜTZ, ERICH und MÜLLER, H.-W. Uber ein neues Zeichen zentralnervöser Erregbarkeitssteigerung im Elektrencephalogramm. *Klin. Wchnschr.*, **1951**, *29*: 22-23.

SHERRINGTON, C. *The Brain and its Mechanism.* Rede Lecture, University of Cambridge, 5 December, **1933**. The Macmillan Company, New York, **1933**, 35 pp.

TRAVIS, L. E., KNOTT, J. R. and GRIFFITH, P. E. Effect of response on latency and frequency of the Berger rhythm. *J. Genet. Psychol.*, **1937**, *16*: 391-401.

Reference: CHATRIAN, G. E., PETERSEN, M. C. and LAZARTE, J. A. The blocking of the rolandic wicket rhythm and some central changes related to movement. *EEG Clin. Neurophysiol.*, **1959**, *11*: 497-510.

PRINTED IN CANADA

PROVOCATION OF ELECTROENCEPHALOGRAPHIC CHANGES IN THE TEMPORAL REGION BY INTERMITTENT ACOUSTIC STIMULI

H. F. R. PRECHTL, Ph.D.

Department of Neurology, University of Groningen, The Netherlands

(Received for publication: March 12, 1958)

In the course of an EEG investigation into central adaptation or habituation to constantly repeated acoustic stimuli, two subjects were found to show pathological paroxysmal waves in the temporal region. On the basis of this incidental finding the question was raised as to whether, and to what extent, acoustic stimuli are capable of provoking pathological waves in the temporal region.

Some data on this problem may be found in the literature. Gastaut, Roger, Corriol and Gastaut (1949) compared the effect of photostimulation with that of intermittent acoustic stimuli of 8-20 c/sec. and a pitch of 1000-8000 c/sec. They found that photostimulation is considerably better suited to the provocation of absences than acoustic stimulation. Arellano, Schwab and Casby (1950) reported on two cases in which epileptic seizures could be provoked with the aid of pure sounds of 100 Db. In 1952 Passouant, Schwab, Brazier and Casby (1952) reported on 13 patients who were stimulated by means of brief intermittent pure sounds while asleep. Four patients showed paroxysmal activity, and a focus was found in three. Kluge and Friedel (1953) made EEG records of 36 normal subjects listening for 15 min. to a tape recording of monotonously repeated drumrolls. The EEG changes then observed consisted of a reduction of the alpha rhythms and the occurrence of theta-waves. Gastaut and Pirovano (1949) reported on four patients and Gastaut, Benoit, Vigouroux and Roger (1954) on two children showing a temporal epileptic focus. In these patients it was possible — by means of clicks or short dashes of pure sound — to produce spikes as a direct reaction. Suenaga and Noda (1955) obtained unilateral EEG leads from the temporal region in 35 test subjects listening to a ticking metronome. The various test subjects showed various changes in the alpha and the beta pattern, according to the prestimulatory picture.

None of the authors mentioned above, however, succeeded in provoking unmistakable changes in the bioelectric activity of the temporal system by acoustic stimulation in a larger number of patients.

MATERIAL AND METHODS

The material used in this investigation consisted of 1500 EEG's made routinely in a total number of 1442 neurological and psychiatric patients. All subjects were submitted to acoustic stimulation in addition to the usual provocations by hyperventilation and intermittent photostimulation. The results of the provocation methods have been compared.

The acoustic stimuli used were clicks of 40-80 Db intensity, produced by a loudspeaker at a distance of about one meter from the patient.

The apparatus used, included an "Epiphote" (Apelimex, Levallois/France) and a device of our own design. The clicks were produced at a rate of 2 per sec. as separate clicks or double clicks. The interval of the double clicks was changed several times. Routine application as a rule involved separate clicks for about 1½-2 min., followed by double clicks for 1 min. This was twice repeated during an EEG recording, with an interval of about 15 min., each time using different leads via the temporal region.

Recordings were made with a Grass III A and a Reega (Alvar), both of the 8-channel type. Leads were bipolar and in addition

by reference against an ear or against an average electrode according to Goldman. All patients were awake, lying on the examining-couch with the eyes closed.

RESULTS

In the group of 1442 patients mentioned above, a total of 1500 EEG's were made. The subjects were patients submitted for routine examination. This group included 139 patients who — once or through several recordings — showed pathological paroxysmal waves in the temporal region, either spontaneously or after provocation. Constant (i.e. non-paroxysmal) focal changes such as delta foci in the case of temporal tumours were not included in the figures given. Nor did these include the occurrence of sleep-patterns or paroxysms not localized in the temporal region such as may be provoked by acoustic stimuli.

The group of 139 patients showing EEG changes was subdivided, according to positive or negative provocative effect of acoustic stimulation (AS), into three subgroups, viz:

(*a*) A group of 130 cases in which AS provoked EEG changes.

(*b*) A group of 8 cases in which AS was not followed by an increased occurrence of paroxysms, although these occurred either spontaneously or due to photostimulation or hyperventilation.

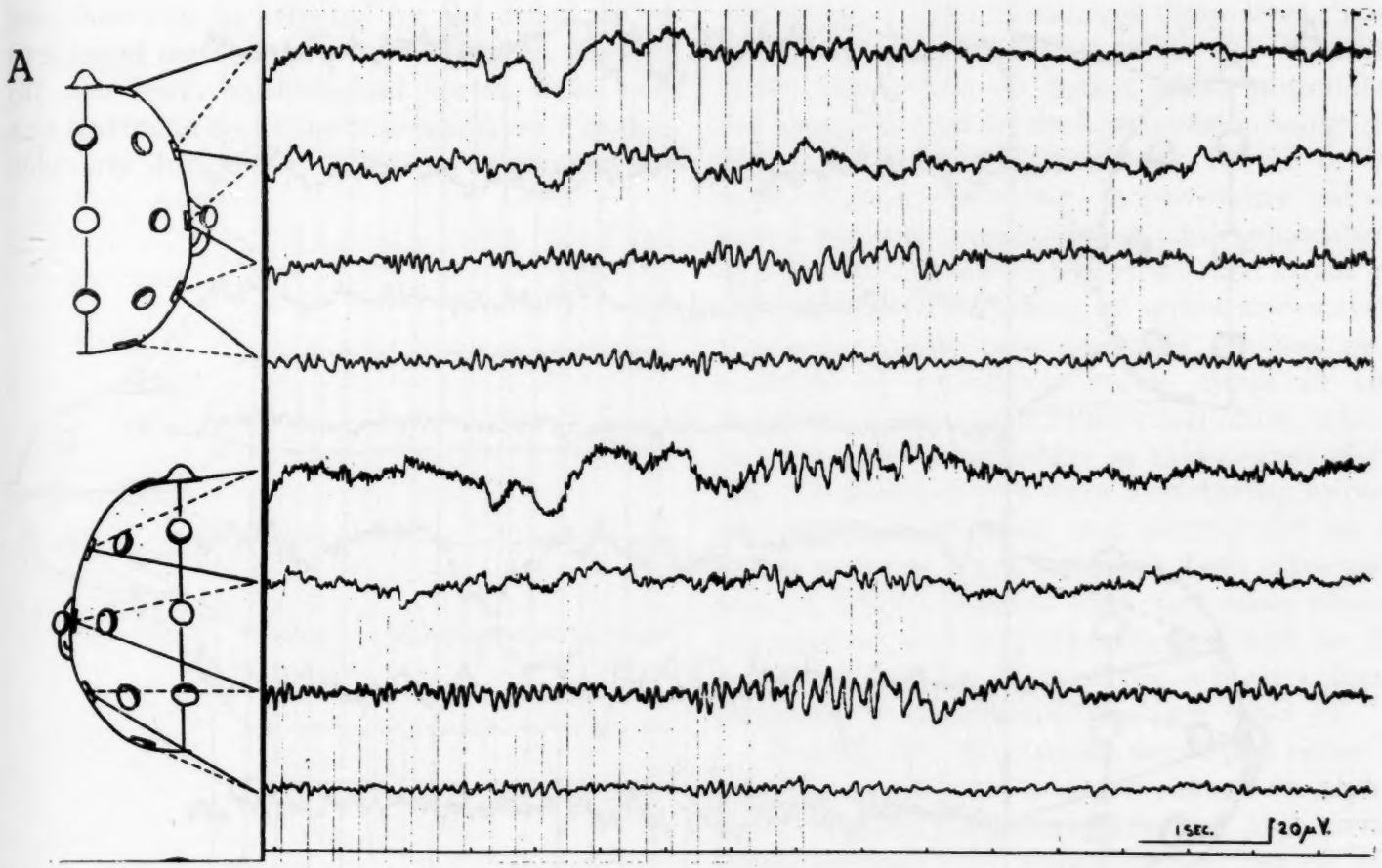
(*c*) One case in which spontaneously occurring spikes were suppressed during AS.

Further differentiation of wave types found spontaneously, due to photostimulation, hyperventilation and AS, in the temporal region, is presented in table I. It may be seen that AS particularly provokes paroxysmal waves with alpha and theta frequencies (fig. 1 and 2) and sharp waves and spikes (fig. 3 and 4) and to a considerably more marked ex-

TABLE I

Correlation between paroxysmal waves in the temporal region and the provocative effect of the acoustic stimuli (130 cases with positive acoustic provocation).

	Spontaneous	Photo-stimulation	Hyper-ventilation	Acoustic stimuli
No abnormalities	101	105	48	—
Paroxysmal waves with α and θ frequencies (fig. 1 and 2)	13	10	40	57
Sharp and slow wave (fig. 3)	3	1	1	14
Delta- or theta waves	5	2	21	3
Spikes or sharp waves (fig. 4)	5	3	8	53
Spikes and waves	3	7	6	3
Provocation to be refrained		2	6	
Seizure during provocation	0	0	4	3
8 cases without acoustic provocation.				
No abnormalities	6	4	1	8
Paroxysmal waves with α and θ frequencies	—	1	3	—
Delta- or theta waves	1	1	3	—
Spikes or sharp waves	1	1	—	—
Spikes and waves	—	1	—	—
Provocation to be refrained			1	
1 case with suppressive effect of acoustic provocation.				
Paroxysmal waves with α and θ frequencies	1	—	1 suppression	



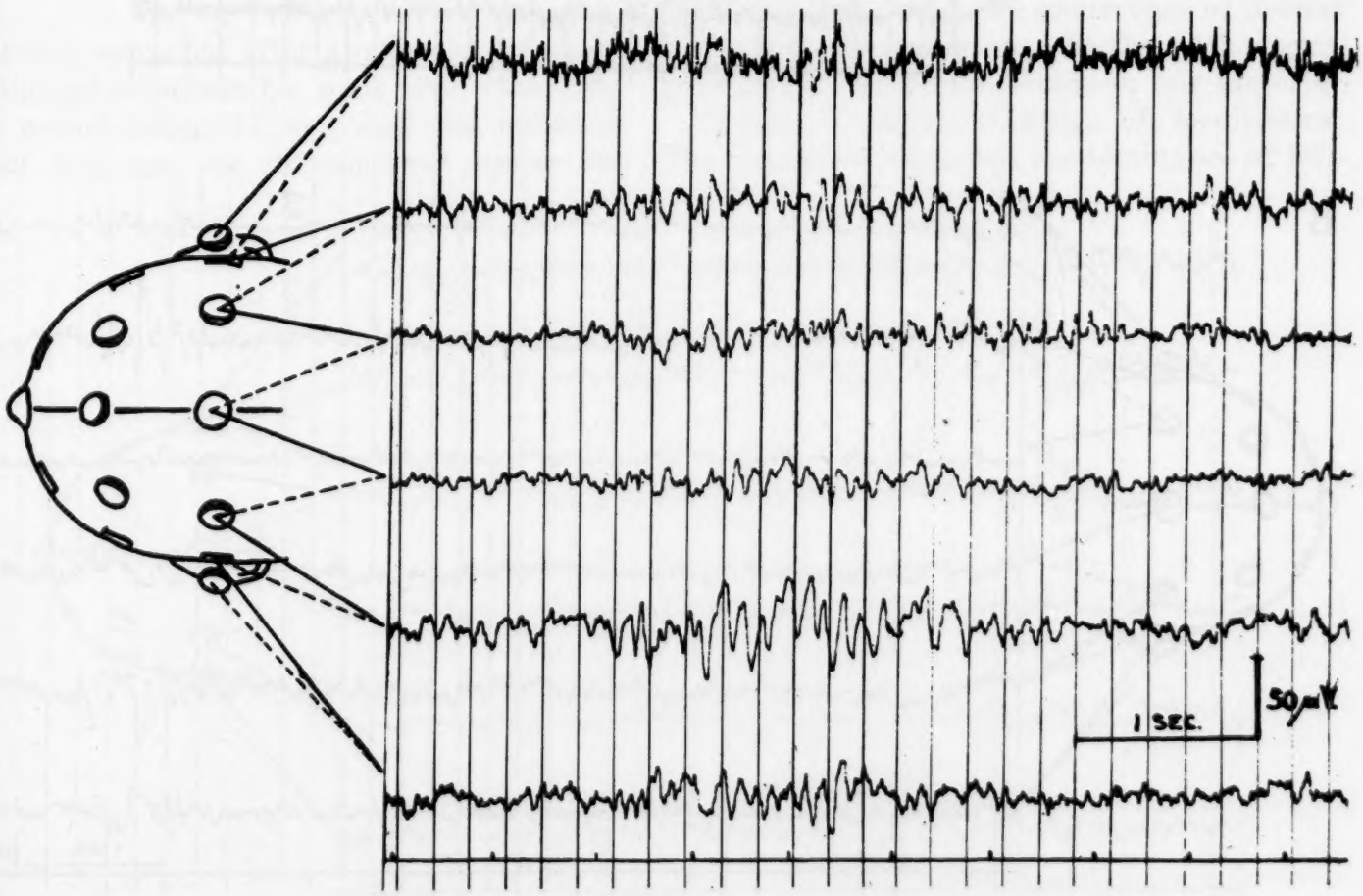


Fig. 1

A-B. Temporal focus of paroxysmal waves with alpha and theta frequencies, marker shows click-frequency. A and B: female, age 34, migraine.

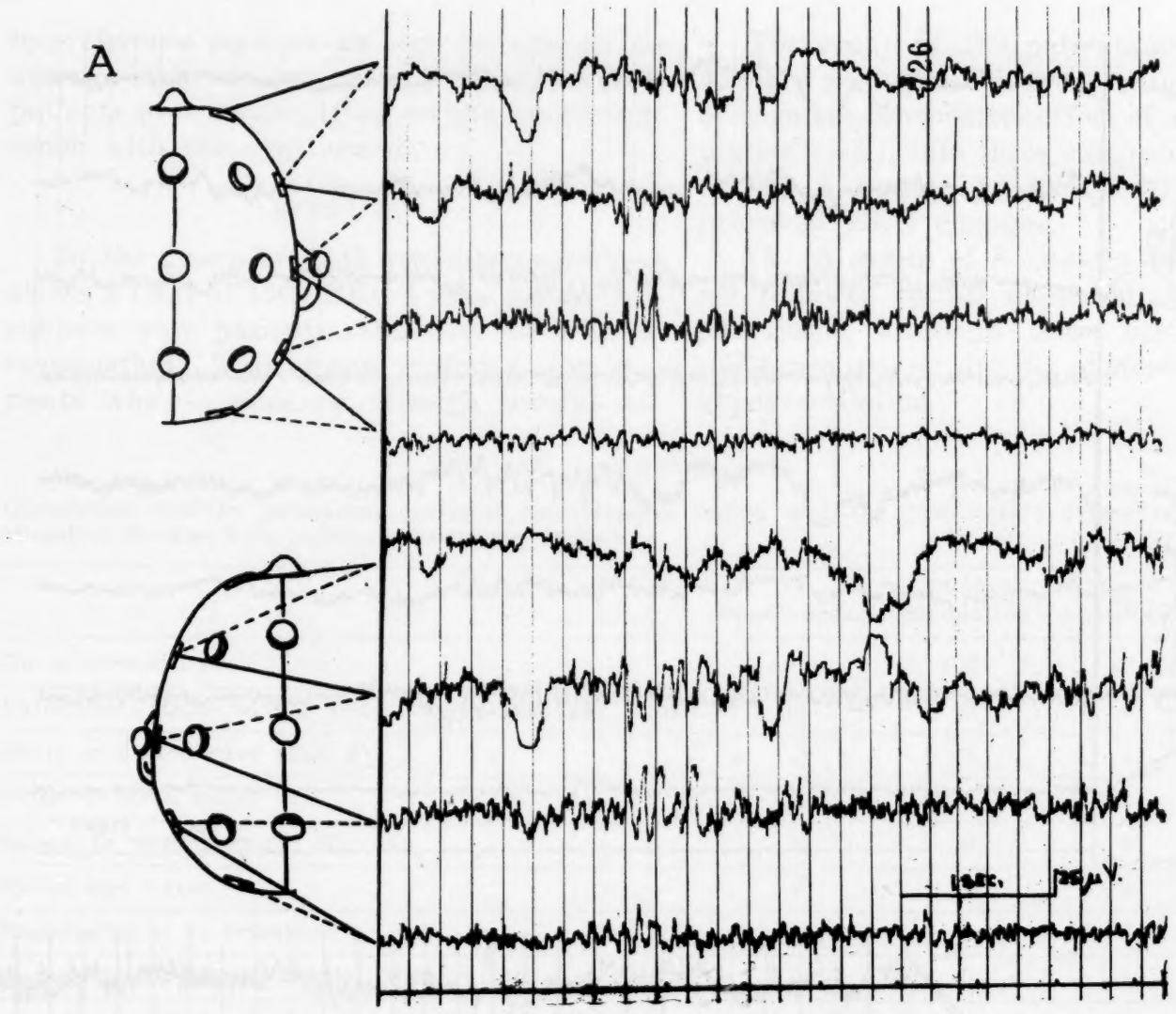


Fig. 2

A-B. Temporal focus of paroxysmal waves with alpha and theta frequencies, markers shows click-frequency. A and B: male, age 41, psychomotor attacks.

tent than can be effected by the other above-mentioned methods of provocation. In 49 cases (37 per cent) pathological waves were seen only during AS (or focus localization was possible only during AS). The provocative effect

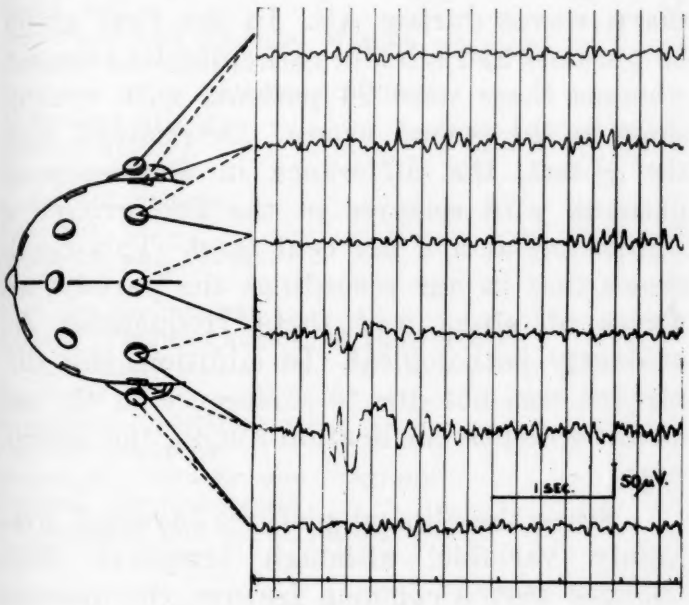


Fig. 3

L temporal focus of sharp and slow waves. Male, age 51. Psychomotor attacks for several years.

invariably occurred after application of clicks in constant sequence for some time (the minimal period being 12 sec., and the maximal period 2½ min. in the material under investigation). The discharges themselves showed no direct correlation with the separate clicks (illus. 1-4) — a fact which eliminates the possibility of evoked potentials being involved. Hyperventilation was found to be more effective, however, in provoking paroxysmal delta and theta-waves, while photostimulation had a somewhat more marked effect on the increased occurrence of spikes and waves. Photostimulation was generally far less provocative of anomalous wave types in the temporal region than hyperventilation, which in turn was less effective in this respect than AS. Clinical seizures were seen during hyperventilation in 4 cases, and during AS in 3. These seizures were temporal both clinically and in EEG features. In a few cases photostimulation and hyperventilation had to be refrained from in view of the subject's unsatisfactory general condition (see table I).

During AS, 20 patients developed either a sleeping rhythm or a slight change in alpha level. Yet it is impossible to find any correlation between the provocative effect of AS and these drowsy states; no unmistakable relationship between the occurrence of drowsy states and the occurrence of the pathological paroxysms was demonstrable in our material.

Table II shows findings of localization. The data show a marked predominance of left-

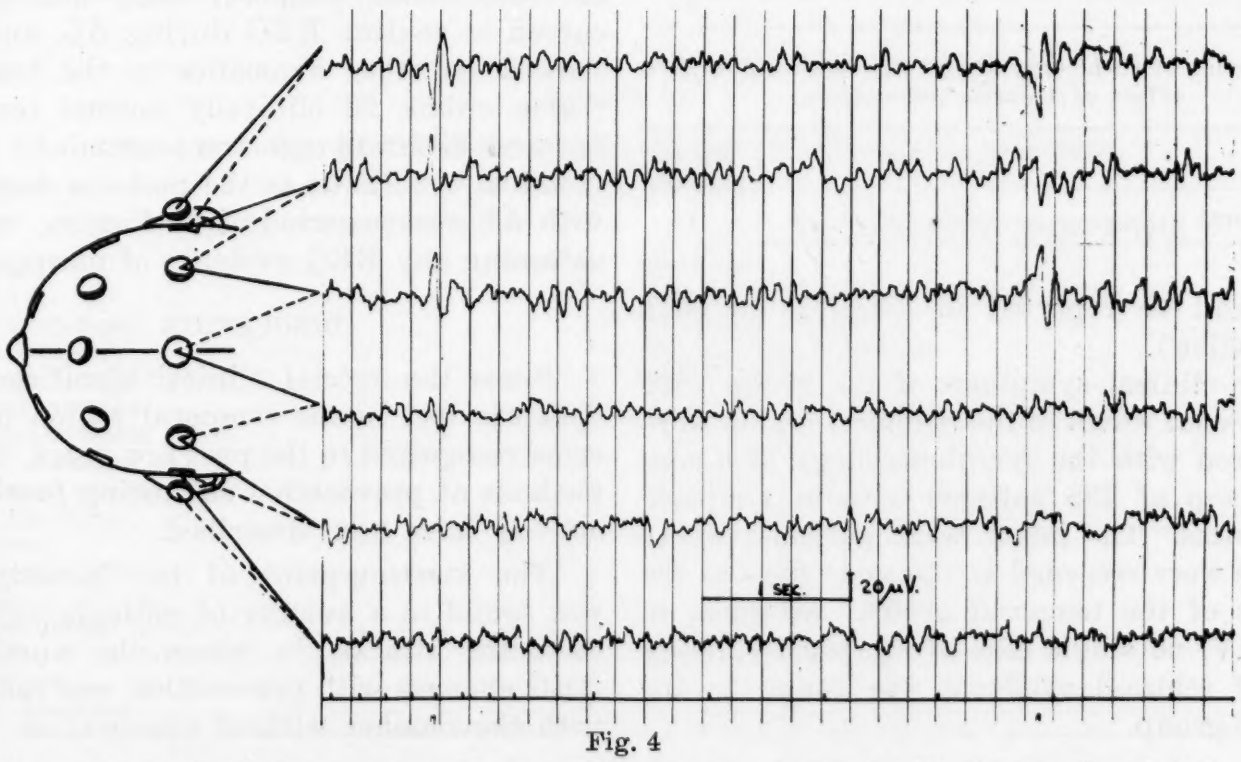


Fig. 4

R temporo-parietal focus of sharp waves. Male, age 12. Aggressive bursts, learning defects.

sided foci, in accordance with the data comprised in the literature.

The age of the patients examined varied between 4 and 68 years, without a significant preference for a special age.

The clinical symptoms in these 139 cases are presented in table III. In patients with predominantly psychiatric conditions, signs of organic lesions have been revealed by psychological tests, independent of EEG findings

TABLE II

Localization of focal activity in 130 cases with positive acoustic provocation.

	No. of patients
Right temporal	18
Left temporal	48
Bitemporal, synchronous	27
Bitemporal	5
R > L	6
L > R	26
	130

Localization of focal activity in 8 cases without acoustic provocation.

	No. of patients
Right temporal	2
Left temporal	3
Bitemporal	2
L > R	1
	8

Localization of focal activity in 1 case with suppressive effect of acoustic provocation.

	No. of patients
Bitemporal	1

(this will be reported in detail in another publication).

The clinical symptoms of the group with paroxysmal waves in the temporal region were compared with the symptomatology of a control-group of 139 patients without temporal paroxysms. The latter were patients, whose EEG's were recorded at the same days as the EEG's of the temporal group. As given in table IV, no single case of temporal epilepsy and of schizoid syndrom was found in the control-group.

In order to get information on the clinical significance of the paroxysmal waves of alpha and theta frequencies, the clinical symptomatology of 50 patients with these waves during AS was compared with the symptomatology of 50 patients showing spikes or sharp waves during AS. In the first group 36 patients had a history of epileptic seizures, whereas there were 24 patients with convulsions in the second group. Determined with the χ^2-test, the difference in frequency of patients with seizures in the two groups is significant at a 2 per cent level. This result shows that in our recordings the paroxysmal waves of alpha and theta frequencies are evidently pathological. In addition, this difference was not due to difference in the use of antiepileptic medication during the recordings.

Since the clinical pictures involved were highly variable, although temporal EEG changes were a common feature, the question arose as to whether the EEG features described did in fact constitute signs of organic cerebral damage, with other common features besides the EEG. In order to eliminate the possibility that the manifestations provoked by AS be based on non-pathological processes, the following procedure was used: In addition to the 1303 patients in whom none of the abovementioned temporal EEG changes occurred at routine EEG during AS, and who showed no other anomalies in the temporal region either, 25 clinically normal test subjects of different age were examined under identical conditions as the patients described, with AS over a period of 30-45 min., without obtaining any EEG evidence of paroxysm.

DISCUSSION

Since the special clinical significance of epileptic foci in the temporal region has become recognized in the past few years, various methods of provocation enhancing focal EEG activity have been described.

The starting-point of the investigations was found in a number of patients with psychomotor attacks, in whom the number of EEG changes with provocation was compared with the number without provocation. Gibbs

TABLE III

Symptomatology of patients with paroxysmal waves in the temporal region.

NEUROLOGICAL SYMPTOMS		PSYCHIATRIC SYMPTOMS	
130 cases with positive acoustic provocation			
Grand mal	17	Schizophreniform syndrome	7
Grand mal and temporal attacks	3	Behaviour disorders (children under 18)	7
Complex temporal attacks	26	Psychopathic behaviour	4
Temporal aura without attacks	1	Neurotic state	11
Abdominal attacks	2		
Ménière attacks	3		
Akinetic seizure	5		
Undefined attacks	9		
Absences	5		
Headache and vertigo	2		
Headache	7		
Migraine-like attacks	10		
Asthma (frequent attacks of many years' standing)	3		
Black out	1		
Meningitis (posttraumatic)	1		
Enuresis nocturna	2		
Narcoleptic attacks and migraine	1		
Cerebral arteriosclerosis	2		
Turrieephaly and syringomyelia	1		
8 cases without acoustic provocation			
Cerebral compression (temporal depressed fracture)	1	Hyperaesthetic emotional syndrome	1
Temporal attacks	1	Hysterical psychopathy	1
Grand mal	1		
Frontotemporal cyst	1		
Twilight states	1		
Undefined attacks	1		
1 case with suppressive effect on the acoustic provocation			
Neurotic state and CO intoxication	1		

TABLE IV

Symptomatology of control-group (139 patients) without temporal paroxysms.

NEUROLOGICAL SYMPTOMS		PSYCHIATRIC SYMPTOMS	
Grand mal	19	Psychosis	8
Petit mal	15	Behaviour disorders (children under 18)	23
Jackson's epilepsy	3	Retardatio mentis	7
Akinetic attacks	2	Psychopathic behaviour	3
Convulsions in children	8	Neurotic state	6
Undefined attacks	5		
Posttraumatic state	5		
Vascular accident	3		
Intracranial tumours	9		
Spastic syndrome	4		
Intoxication	1		
Leuco-encephalitis	1		
Migraine	5		
Atypic headache	5		
Asthma	2		
Chorea minor	1		
Enuresis nocturna	4		

and Gibbs (1946) found 25-31 per cent epileptic discharges in the EEG in epileptics with temporal attacks while awake; the corresponding figure during natural sleep was 98 per cent. In the case of Evipan anaesthesia, too, several investigators have reported activating effects (see Kajtor 1956, 1957).

More recently, several laboratories have used Largactil intravenously as provocation (Mayer and Lechner 1954; Fünfgeld 1956). Gloor *et al.* (1957) recently pointed out that, when pharyngeal electrodes are used, sleep provocation is obviated in a high percentage of cases.

Metrazol (Cardiazol) and Megimide, sometimes with simultaneous photostimulation, have also been used in focal diagnosis (Johnson and Walker 1952, and others).

Our results cannot be directly compared with these investigations, as our series included not only patients with psychomotor disturbances but also patients with other clinical symptoms. The results obtained were not selected according to a certain clinical picture but rather according to the EEG evidence of paroxysmal discharges in the temporal region; differentiation was subsequently made on the basis of whether pathological discharges occurred spontaneously or only after photostimulation, hyperventilation and AS. The figures given in table I clearly demonstrate the superiority of AS as compared with the other routine provocations by photostimulation and hyperventilation. In 37 per cent of patients focal diagnosis was possible only by AS, although pharyngeal electrodes were used.

Some indications are available as to the neurophysiological mechanism of the provocative effect of AS on pathological discharges in the temporal region. It has been established with certainty that the afferent bombardment caused by the clicks in the auditory cortex and in other parts of the temporal region [1] should last at least several seconds before an effect occurs. The afferent impulses would seem to activate epileptic activity to the extent that it becomes visible in the EEG. A certain correlation with habituation processes may be suspected also: at the beginning of serial stimulation there is as a rule an arousal reaction for 5-10 sec., with simultaneous suppression of epileptic discharges, while subsequently there is a return to the alpha level, followed by epileptic discharges. This occurs only, however, if the clicks are repeated at a low and constant frequency. Frequencies of 1½-3 per sec. proved to be the most effective. In our experience provocation remained absent at higher frequencies. It may be stated again that no correlation exists between the activation of pathologic paroxysms and the occurrence of sleep or drowsy states during AS.

1 Machne and Segundo (1956), using micro-leads in the amygdaloid nucleus, found units which responded to clicks by series of discharges.

SUMMARY

1. From 1500 routine EEG's, 139 were selected as showing paroxysmal changes in the temporal region. During all (1500) EEG recordings provocation was attempted by photostimulation, hyperventilation and by intermittent acoustic stimulation.

2. The clicks were applied for about 3 min., at an average frequency of 2/sec. and an intensity of 40-80 Db.

3. Clicks had an activating effect in 130 of the 139 cases with temporal paroxysms in the EEG. In 49 cases (37 per cent) pathological waves were seen only during clicks, or localization of focus was possible only during clicks.

4. The mechanism of the provocative effect of acoustic stimulation is discussed.

RÉSUMÉ

1. Sur 1500 EEG de routine on a choisi 139 comme étant démonstratifs de changements paroxystiques dans la région temporale. Au cours de tous (1500) les EEG la stimulation fut essayée au moyen de la stimulation lumineuse, l'hyperventilation, et la stimulation auditive intermittente.

2. Les clics étaient appliqués pendant environ 3 min., à une fréquence moyenne de 2/sec. avec une intensité de 40 - 80 Db.

3. Les clics avaient un effet activant dans 130 des 139 cas de paroxysmes temporaux. Chez 49 cas (37 pour cent) on n'a vu des ondes pathologiques qu'au cours des clics,

ou bien la localisation du foyer n'était possible qu'à ce moment-là.

4. On discute les mécanismes de l'effet provoquant de la stimulation auditive.

ZUSAMMENFASSUNG

1. Aus 1500 routinemässig aufgenommenen Elektroencephalogrammen wurden diejenigen ausgewählt, die paroxysmale Wellen in der Temporalregion aufwiesen; es waren dies 139. Bei sämtlichen (1500) EEG-Aufnahmen wurde mit Flackerlicht, Hyperventilation und Serien von Clicks provoziert.

2. Die Clicks wurden meist 3 Minuten lang mit einer Durchschnittsfrequenz von 2/sec und einer Intensität von 40 - 80 Db. geboten.

3. Bei 130 von den 139 Fällen hatten die Clicks provozierenden Effekt auf die paroxysmalen Entladungen im Temporalgebiet. Bei 49 Fällen, das sind 37 Prozent, traten nur während der Clicks pathologische Wellen auf oder es war nur dann eine Lokalisation des Krampffocus möglich.

4. Der neurophysiologische Mechanismus des provozierenden Effekts wird diskutiert.

The author wishes to express his thanks to A. M. Hamoen, M.D., for his criticism on the interpretation of the electroencephalograms and to the T.N.O. (Netherlands) for a grant which partly supported this work.

REFERENCES

ARELLANO, A. P., SCHWAB, R. S. and CASBY, J. U. Sonic activation. *EEG Clin. Neurophysiol.*, **1950**, *2*: 215-217.

FABISCH, W. The effect of chlorpromazine on the EEG of epileptic patients. *J. Neurol. Neurosurg. Psychiat.*, **1957**, *20*: 185-190.

FÜNFGELD, E. W. Zur Frage der Megaphenprovokation bei der Elektrencephalographie. *Arch. Psychiatr. Zschr. Neurol.*, **1956**, *194*: 571-583.

GASTAUT, H. J., BENOIT, P. H., VIGOUROUX, M. et ROGER, A. Potentiels évoqués par des stimuli auditifs sur la région temporale de certains épileptiques. *EEG Clin. Neurophysiol.*, **1954**, *6*: 557-564.

GASTAUT, H. e PIROVANO, E. Epilessia indotta da stimulatione uditiva intermittende ritmica o epilessia psofogenica. *Arch. Psicol. Neurol. Psichiat.*, **1949**, *10*: 297-316.

GASTAUT, H., ROGER, J., CORRIOL, J. and GASTAUT, Y. Epilepsy induced by rhythmic, intermittent, auditory stimulation or epilepsy ''psophogenique''. *EEG Clin. Neurophysiol.*, **1949**, *1*: 121.

GLOOR, P., TSAI, C., HADDAD, F. and JASPER, H. H. The lack of necessity for sleep in the EEG or ECG diagnosis of temporal seizures. *EEG Clin. Neurophysiol.*, **1957**, *9*: 379-380.

JOHNSON, H. C. and WALKER, A. E. Response of experimental epileptic foci to intravenous and topical Metrazol. *EEG Clin. Neurophysiol.*, **1952**, *4*: 131-139.

KAJTOR, F. Aktivierung und Analyse der steilen Wellen und Krampfspitzen in Evipannarkose bei Temporallappen - Epilepsie. *Arch. Psychiatr. Zsch. Neurol.*, **1956**, *194*: 238-262.

KAJTOR, F., HULLAY, J., FARAGO, L. and HABERLAND, K. Effect of barbiturate sleep on the electrical activity of the hippocampus of patients with temporal lobe epilepsy. *EEG Clin. Neurophysiol.*, **1957**, *9*: 441-451.

KLUGE, E. und FRIEDEL, B. Uber die Einwirkung einförmiger akustischer Reize auf den Funktionszustand des Gehirns. *Zsch. Psychotherapie*, **1953**, *3*: 212-226.

MACHNE, X. and SEGUNDO, J. P. Unitary responses to afferent volleys in amygdaloid complex. *J. Neurophysiol.*, **1956**, *19*: 232-240.

MAYER, F. und LECHNER, H. Zur Frage der Provokation bei Temporallappen - Epilepsie im EEG. *Wien. klin. Wschr.*, **1954**: 903-906.

PASSOUANT, P., SCHWAB, R. S., BRAZIER, M. A. B. and CASBY, J. Activation of the EEG during sleep with regular repetitive sounds every 2 to 10 seconds. *EEG Clin. Neurophysiol.*, **1952**, *4*: 382-383.

SUENAGA, K. and NODA, K. Responses of temporal EEG of man to intermittent sound stimuli. *Kirume Med. J.*, **1955**, *2*: 42-50.

VIGOUROUX, M., BENOIT, P. and GASTAUT, H. Evoked potentials by auditory stimuli in the temporal region in an epileptic patient. *EEG Clin. Neurophysiol.*, **1954**, *6*: 163-164.

Reference: PRECHTL, H. F. R. Provocation of electroencephalographic changes in the temporal region by intermittent acoustic stimulation. *EEG Clin. Neurophysiol.*, **1959** *11*: 511-519.

PRINTED IN CANADA

ANNOUNCEMENT

INCREASED SUBSCRIPTION RATES FOR THE EEG JOURNAL

Continued rise in cost of printing and engraving, together with the increase in number of pages in each volume of our Journal, made necessary by the large amount of scientific material submitted for publication, has made it necessary to raise the rates of annual subscriptions for the coming year (1960).

Please note in making your renewal for 1960 that the regular rate will be thirteen dollars ($13.00 Canadian). Subscriptions through EEG Societies will be increased to twelve dollars ($12.00 Canadian).

This increase in income should make it possible not only to eliminate financial deficits but to provide over 900 pages of scientific material in the forthcoming volume of our Journal. In this way we hope to reduce present delays in publication.

The Editorial Board expresses appreciation for the continued support of a steadily increasing numbers of subscribers.

ELECTROCORTICOGRAPHIC CHANGES IN TEMPORAL LOBE EPILEPSY AT REST AND DURING INDUCED SLEEP

PIERO ROVETTA, M.D.

Divisione di Neurochirurgia, Ospedale Maggiore, Bologna, Italy

(Received for publication: May 13, 1958)

INTRODUCTION

By electrocorticographic studies and surgical operations on epileptic patients with temporal lobe foci it has been possible in many cases to locate precisely the origin of the seizure discharges. Direct registrations from the lateral surface of the temporal lobe generally permit to record epileptic waves from an extensive cortical area rather than from a circumscribed point. This extensive cortical area involves the three lateral convolutions, the tip of the lobe and the opercular region of the insula (Bailey and Gibbs 1951; Green, Duisberg and McGrath 1951; Jasper, Pertuisset and Flanigin 1951; Gastaut *et al.* 1950, 1953; Guillaume, Mazars and Mazars 1953; Petit-Dutaillis *et al.* 1953; Paillas, Gastaut *et al.* 1953; Krayenbühl, Hess and Weber 1953; Maspes and Marossero 1954; Falconer *et al.* 1955).

The paroxysmal electric alterations may appear alternatively at different points on the temporal cortex (Bailey and Gibbs 1951; Jasper, Pertuiset and Flanigin 1951; Gastaut *et al.* 1953; Petit-Dutaillis *et al.* 1953; Maspes and Marossero 1954). Important evidence has been obtained by the use of depth electrodes inserted into the temporal lobe. The authors who have used this technique have been able to record spontaneous spike discharges in deep regions situated near the base of the temporal lobe and the hippocampal gyrus (Green, Duisberg and McGrath 1951; Krayenbühl, Hess and Weber 1953; Amador 1955; Kellaway 1956; Kendrick and Gibbs 1957) and also from the region of the amygdaloid nucleus (Paillas, Vigouroux, Corriol and Bonnal 1952; Gastaut *et al.* 1953; Brazier *et al.* 1954 and 1956).

Other authors, placing surface electrodes in contact with the base of the temporal lobe and the hippocampal gyrus, have been able to establish in many cases that the epileptogenic focus was situated in these structures (Paillas and Gastaut 1950; Paillas, Gastaut *et al.* 1953; Marshall 1953; Valladares and Markovich 1953; Falconer, *et al.* 1955). These last reports tend to demonstrate that the origin of the epileptic discharges may be deep in the temporal lobes or in the "rhinencephalic" structures. This point of view appear to be confirmed by the observation of almost all the authors named above that the epileptic discharges in the hippocampal gyrus, in Ammon's horn and in the amygdala persisted after the partial ablation of the temporal lobe (as Jasper and Kershman 1941 had already observed). According to certain authors, the insula may be primarely involved by the epileptogenic lesion in some cases (Guillaume and Mazars 1948 and 1953; Paillas, Gastaut, Bonnal and Vigouroux 1953; Penfield and Jasper 1954; Bailey 1954; Amador 1955); sometimes also the orbital region of the frontal lobe may be involved (Gastaut *et al.* 1953).

Finally it is not without importance to recall that in certain cases electrocorticography of the lateral surface of the temporal lobe did not reveal epileptic activity (Penfield and Flanigin 1950; Green, Duisberg and McGrath 1951; Gastaut *et al.* 1953; Guillaume, Mazars and Mazars 1953; Krayenbühl, Hess and Weber 1953) and that the local applica-

tion of Metrazol (Cardiazol) has sometimes not produced modifications of preexisting epileptic activity (Bergamini, Marossero and Maspes 1953).

Recently Gastaut *et al.* (1953) have further developed the concept of the deep origin of the discharges of a temporal focus in epileptics. These authors assert that the primary focus at times may not be situated in the "rhinencephalic" cortex but in deeper structures such as the thalamus, hypothalamus and tegmentum. In these cases a scalp EEG would show discharges emanating alternatively from points in one or the other of the temporal lobes as Lennox and Brody (1946) demonstrated in cases of subcortical lesions. Dell (1953) and Kaada (1953) also expressed ideas along this line. The hypothesis of the subcortical (diencephalic) origin of focal type temporal discharges was admitted as plausible by Broglia, Marossero and Maspes (1954) in cases with spike discharges from the posterior temporal region.

The purpose of this study is to report on the results of electrocorticographic examinations carried out in the course of operations performed for temporal lobe epilepsy.

METHODS

Eighteen subjects were examined, almost all of whom were young or middle aged. These subjects demonstrated seizures of a psychomotor type, of a generalized type, or of a psychomotor and generalized type. Only one patient showed signs of neurological deficit (spastic hemiparesis on the side contralateral to the epileptic focus). The pre-operative EEG revealed in all cases focal spike discharges in wakfulness as well as in sleep obtained with a dose of Pentothal equal to that used during electrocorticography (see below). In 7 cases these discharges were strictly localized on one side. They showed occasional spread to the homologous contralateral region in 10 cases, while in only one case the temporal discharges shifted in successive tracings from one side to the other. In all but one case unilateral anterior temporal lobectomy (right or left) was carried out and in the case with shifting bi-temporal discharges a bilateral operation was performed (Prof. M. Milletti).

TECHNIQUE

Arrangement of electrodes.

In every case (generally 40-47) electrodes were applied both sub- and supra-durally.

The electrodes were made of silver or platinum buttons 4-5 mm. in diameter and 0.5 mm. thick. These were incapsulated in polyethylene sheets and attached to thin flexible wires. The wires were perfectly insulated and inserted in polyethylene tubes. Six (rarely 5) electrodes were placed in a linear arrangement in contact with the hippocampal gyrus.[1]

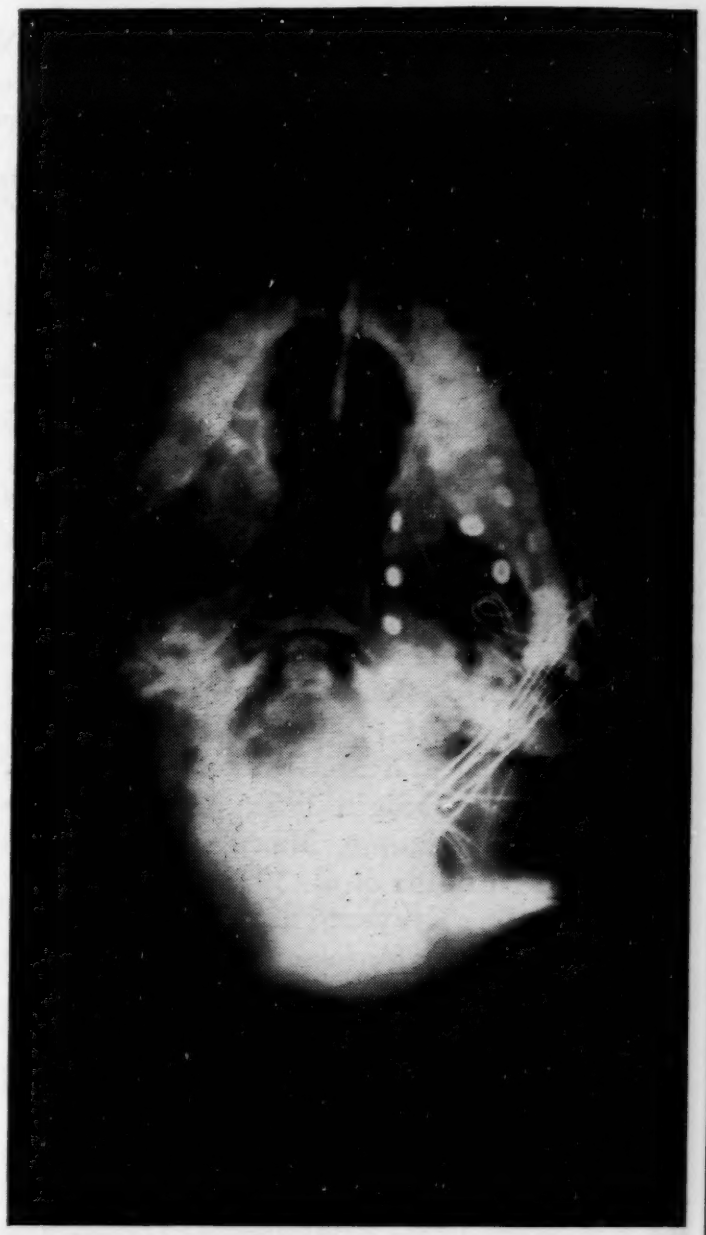


Fig. 1
X-ray of the skull showing electrode positions.

[1] The terms hippocampal gyrus and uncinate gyrus are used interchangeably to designate the convolution of the hippocampus.

Four electrodes were placed on the tip of the temporal lobe; 2 to 4 electrodes were arranged above and below the sylvian fissure and in some cases 2 electrodes were placed on the lateral surface of the temporal pole. Occasionally another electrode was placed subdurally in contact with the posterior orbital surface of the frontal lobe. The remaining electrodes, 30 in number, were arranged epidurally in 5 transverse rows of 6 electrodes each, in such a manner as to correspond to the fusiform gyrus, to the 3 lateral temporal convolutions and to the inferior part of the suprasylvian region. In one case all the electrodes were placed below the dura. After the closure of the osteoplastic wound, the electrodes were left in position for a period ranging from 24 to 48 hours prior to the removal of the temporal lobe. The placement of electrodes was controlled in every case by means of X-rays taken in the AP, lateral and axial projections (fig. 1), and was directly controlled at the time of the second operative stage. For further details see Milletti (1955 and 1959).

The registrations were made with electroencephalographs of 6-8 (A.T.E.) or 16 (Ediswan) channels. The electrode resistence was generally not higher than 4,000 ohms. All ECoG examinations were carried out with the patients awake for a period of from 3-6 hours and in 15 cases during sleep rapidly induced with Pentothal at doses of 75-300 mg. In 14 cases registrations were also carried out before and during surgical anesthesia: the analysis of the results of this last study has already been separately described (Rovetta and Suriani 1956).

RESULTS

A — *Spontaneous epileptiform activity.*

1. *Resting activity.* Sixteen cases (or 89 per cent) showed maximum epileptic activity composed of triphasic spikes, and rarely of slow biphasic potentials in the hippocampal gyrus, mostly in its anterior portion. The amplitude generally did not exceed 500 μV. and rarely 800 μV. Often spikes were obtained from two or more electrodes on the hippocampal gyrus, but mostly there was phase reversal in only one or two of the three more anteriorly situated electrodes (fig. 3, 6, 7). Discharges on the middle and posterior portion of the uncinate gyrus were sometimes asynchronous with the discharges of the more anterior part. In the remaining two cases only a few spikes of 150 μV. or less were recorded from the hippocampal gyrus.

In all cases spike discharges were obtained from the temporal pole and in some instances from the frontal and temporal operculum. These in general consisted of potentials having a duration of 200 msec. or more and the amplitude did not exceed 300 μV. in all but 5 cases in which the spikes were higher than those recorded from the uncinate gyrus. With the exception of 2 cases, the number of spikes per time unit was less than that recorded from hippocampal gyrus. In one case in which an electrode was also applied to the orbital surface of the frontal lobe, paroxysmal discharges were obtained from this region with characteristics of duration, amplitude and appearance equal to those from the tip of the temporal lobe. The spike discharges of the temporal pole were sometimes synchronous with those of the hippocampal gyrus but in a greater number of cases the discharges occurred independently in the two regions (fig. 2).

In many cases discharges also spread over the fusiform gyrus and all three lateral convolutions, but in 5 patients they were obtained only from limited areas of one or two lateral convolutions. Discharges did not appear in 5 instances on the fusiform gyrus and in one on the lateral aspect of the temporal lobe. From the frontal and parietal operculi spikes were recorded in 3 cases. The spike amplitude was generally not above 150 μV. and in almost all patients the paroxysmal potentials were rare as compared to the frequent occurrence in the other region examined. In some cases no more than 3-4 discharges were observed in almost half an hour of recording. In one patient only the spikes predominated on the three lateral convolutions.

The epileptiform potentials of the fusiform gyrus and the lateral aspect of the

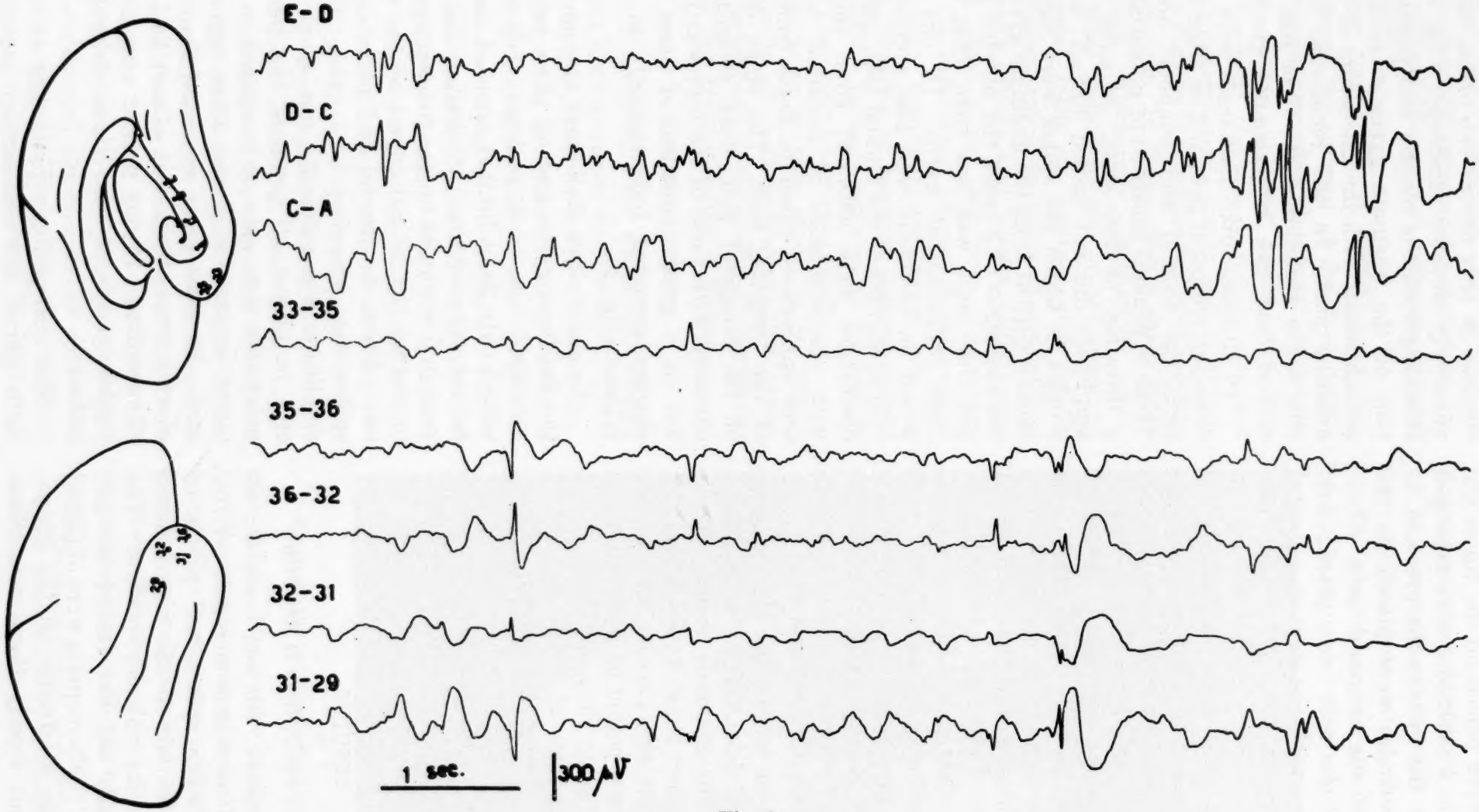


Fig. 2

Right temporal lobe epileptogenic focus; patient awake. Records obtained from the points indicated. On the hippocampal gyrus (electrodes indicated with letters) a higher frequency of discharges and a greater amplitude of the spikes is observed. The spikes from the temporal pole (electrodes indicated with numbers) are usually asynchronous with the discharges from the hippocampal gyrus.

lobe were
with the
number
in differ

lobe were usually synchronous and often also with the discharges from the pole. In a small number of cases, spikes appeared alternatively in different zones of the three lateral convolutions. When the discharges from the pole were synchronous with those of the uncinate gyrus, the spikes from the lateral surface were also occasionally synchronous.

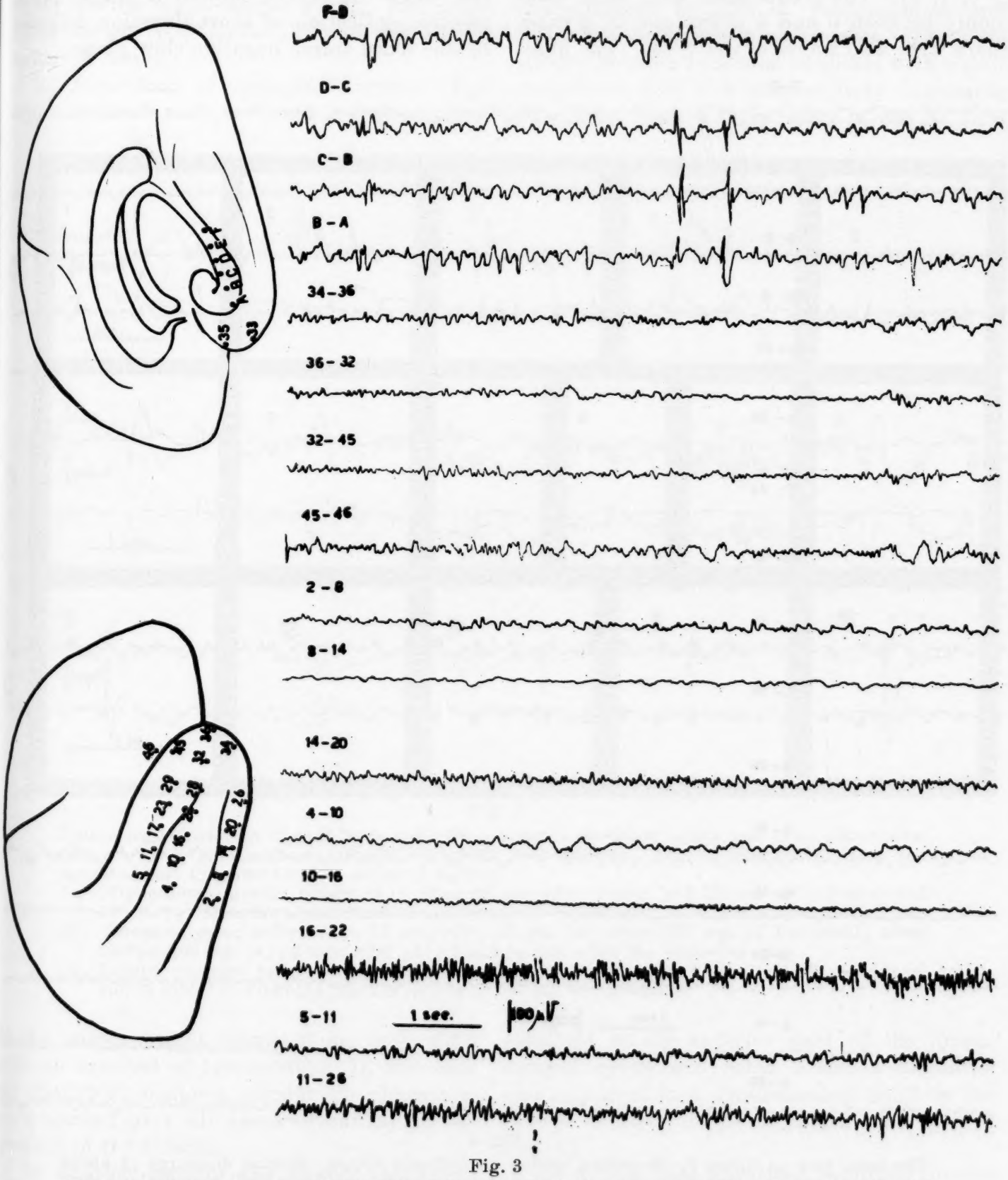


Fig. 3

Right anterior temporal epileptogenic focus. Recording after awakening from barbiturate sleep; spike discharges of high amplitude limited to the anterior end of the hippocampal gyrus; some slow activity and diffuse fast rhythms due to the residual effect of Pentothal.

2. *Slow activity and rapid rhythms.* In all cases waves of low frequency were observed in all examined regions and most notably on the hippocampal gyrus and the pole (fig. 2, 3, 6, 7, 9). The frequencies were most commonly between 6 and 4 c/sec. and in 8 cases there were also waves of 3-2 c/sec. The amplitude varied from 50 to 150 μV. and in one case it was as high as 250 μV. in all leads. This slow activity of theta and delta frequencies usually appeared in trains and in a few cases the waves showed a slight initial positive deflection of short duration followed by the more ample negative slow phase.

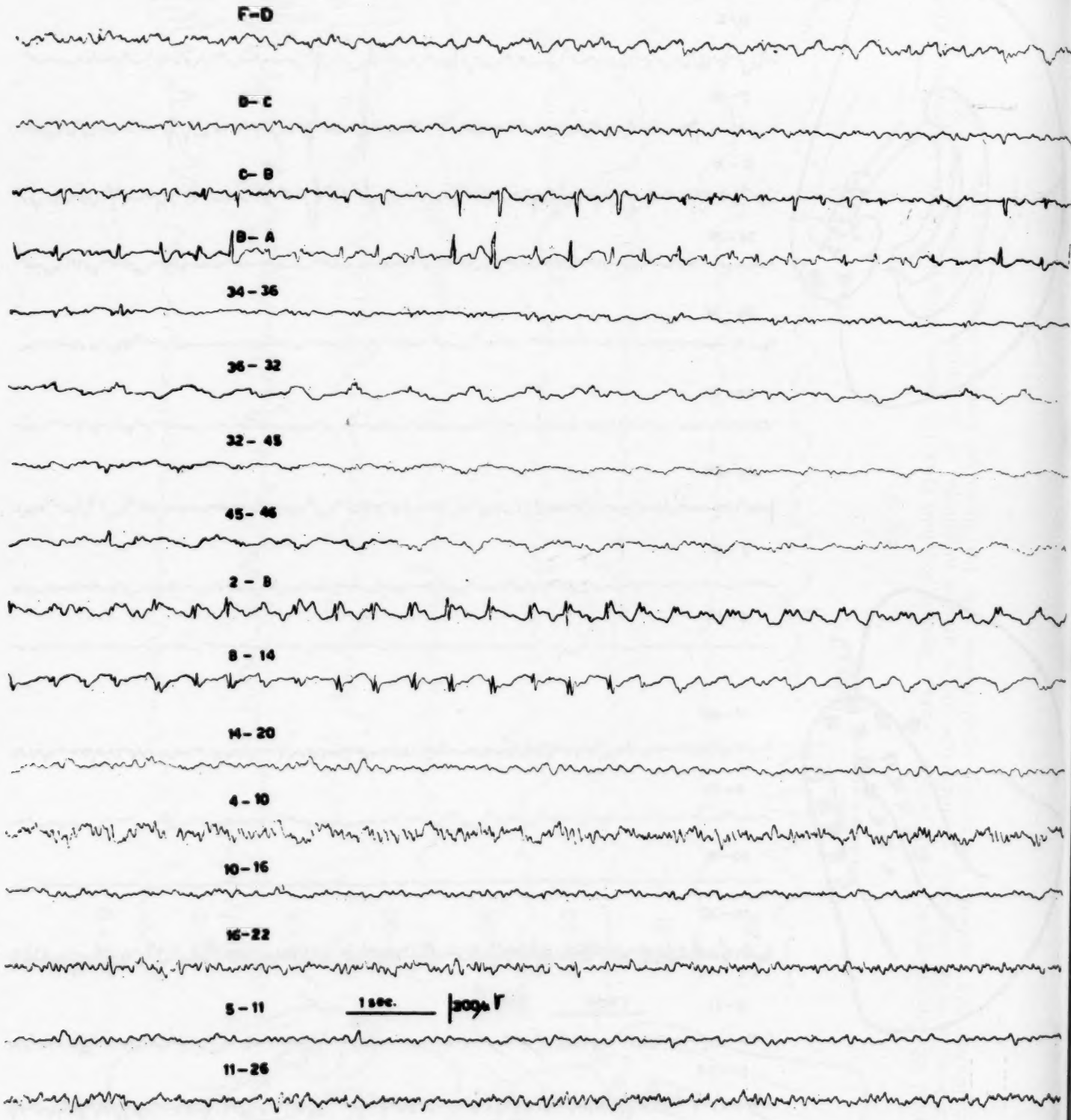


Fig. 4

The same case as figure 3. Recording during an epileptic attack. Seizure discharge at about 2 c/sec. on anterior hippocampal gyrus and posterior part of third temporal convolution; slow activity in posterior hippocampal gyrus and temporal pole; no changes of the rhythm in the other parts of the lateral surface.

Rapid sinusoidal rhythms, generally of 15-18 c/sec., and more rarely of 12-14 or 20-24 c/sec., were clearly observed in 16 cases. They were more numerous and sometimes higher on the hippocampal gyrus. The amplitude varied from 25-60 μV. and was rarely higher or lower.

3. *Recording of epileptic seizures.* Epileptic seizures were recorded 5 times:: twice of spikes with increasing amplitude and with diminishing frequency from 5-3 c/sec.

The fourth attack was observed during voluntary hyperventilation and was clinically characterized by loss of consciousness and automatic swallowing movements. The electrical discharge consisted of spikes with a slow component and with progressively decreasing frequency from 5-1 per sec.; it was at first

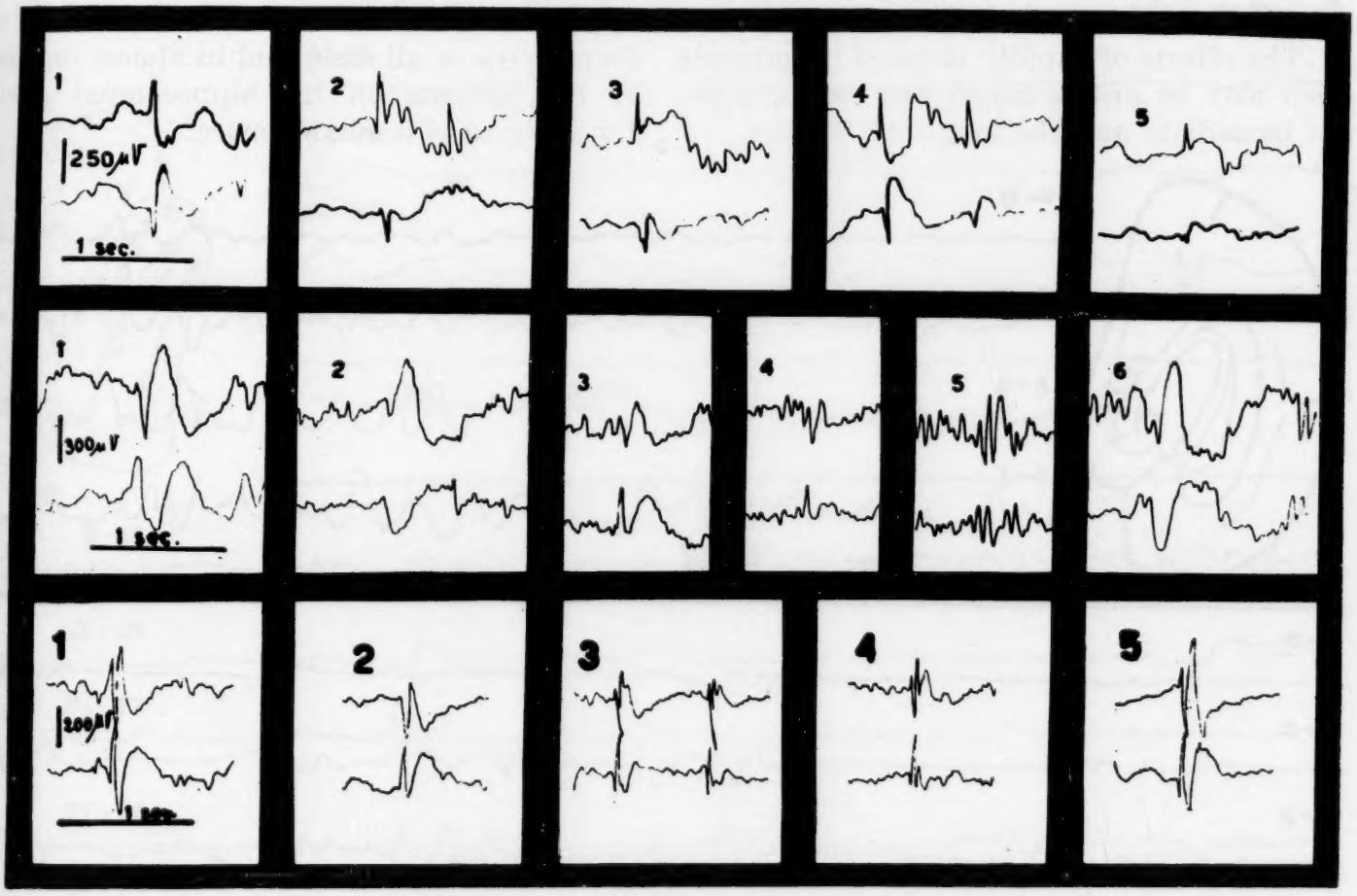


Fig. 5

Spikes registered with bipolar leads and with a common electrode before and after administration of Pentothal in three cases of temporal lobe epilepsy. The calibration of time and amplitude are the same for each series of figures.

(a) Hippocampal gyrus: before (1); after 25 sec. (2); 1 min. and 30 sec. (3); 2 min. and 12 sec. (4) from the administration of 150 mg. of Pentothal; (5) 30 sec. after other 150 mg.

(b) Temporal pole: before (1); 15 sec. (2); 35 sec. (3) after 200 mg. of Pentothal; after further 100 mg. (4); 2 min. later (5); 1 and ½ min. after the preceding (6).

(c) Lateral surface: before (1) and after 20 sec. (2), 40 sec. (3), 1 min. and 40 sec. (4), 4 and ½ min. (5) from the rapid injection of 200 mg. of Pentothal.

in the same patient operated on both sides with an interval of two months. In this case the electrical seizures, similar in character, were spread over all areas examined at the moment of the attacks.

In another patient the seizure discharge was strictly localized to the infero-medial portion of the temporal pole and was made up localized to the anterior part of the hippocampal gyrus and after 2 sec. a discharge also appeared in a circumscribed point on the lateral surface of the temporal pole (fig. 3 and 4).

In a fifth case an attack occurred during a period of spontaneous drowsiness. The spike discharges were initially localized to the

hippocampal convolution and to a circumscribed point of the first temporal gyrus. After 20 sec. a discharge also appeared in the middle lateral convolution. The spikes of this second discharge were not synchronous with those of the hippocampal gyrus and stopped 10 sec. after the extintion of the latter.

B — *Effects of Pentothal on the paroxysmal activity* (15 cases).

The effects of rapidly induced barbiturate sleep may be distinguished into two groups: the immediate and the long-term effects.

the spikes also decreased to levels below 50 to 75 per cent of the original values (fig. 5 and 8). Complete disappearance of paroxysmal activity was noted in one instance on the hippocampal gyrus and in 6 cases in the regions of the pole, the fusiform gyrus and the lateral convolutions for a period of 2 min. In 4 cases the characteristics of spike amplitude and duration remained unchanged on the uncinate gyrus. The slow waves disappeared on the lateral aspect and the fusiform gyrus in all cases and in almost one half of the patients on the hippocampal gyrus, for a period of 5 min. or more.

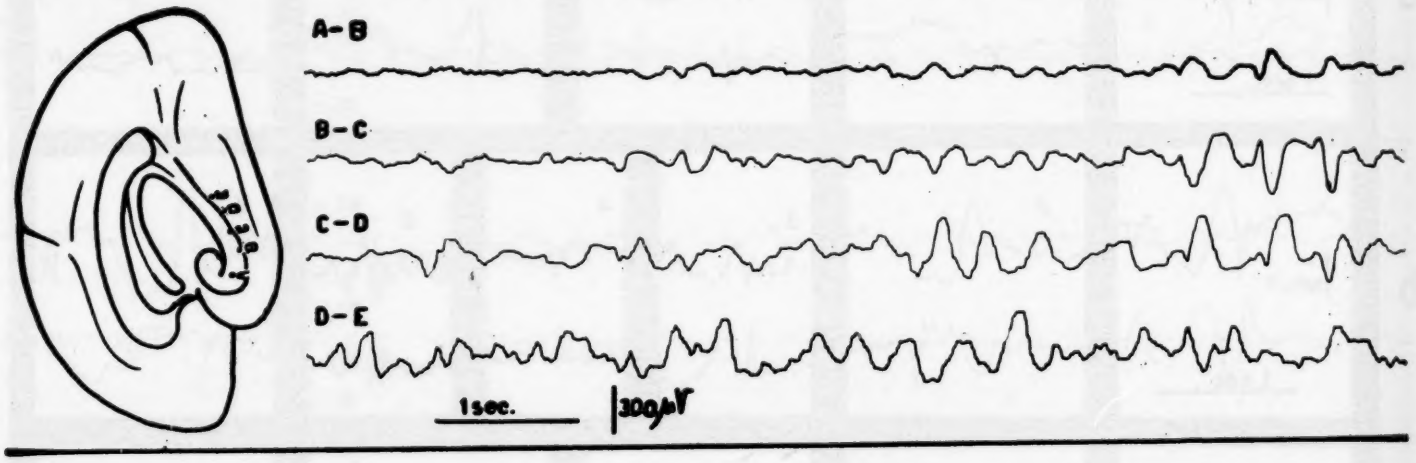


Fig. 6

Right anterior-temporal epileptogenic focus: Recording from the hippocampal gyrus with patient awake (upper tracing) and after injection of 200 mg. of Pentothal (lower tracing). During barbiturate sleep the discharges appear with intervals of 1-2 sec. and are simultaneous with bursts of fast waves. Depression of slow activity is also noticed. (Time and amplitude calibration the same for the two records.)

The first was observed immediately after the injection of Pentothal together with loss of consciousness and when the patients were not roused by noxious stimuli: it was characterized by depression of the epileptic activity. The amplitude of the spikes diminished from 15 to 75 per cent on the hippocampal gyrus and from 25 to 60 per cent in the other regions. The total duration of

The second group of effects was observed from one to 3 min. after the injection of the drug and generally during the period when the amplitude and duration of the spikes had not as yet completely returned to their original values. At this time the patients were generally in light or medium deep sleep; barbiturate spindles appeared simultaneously or just before the changes here described

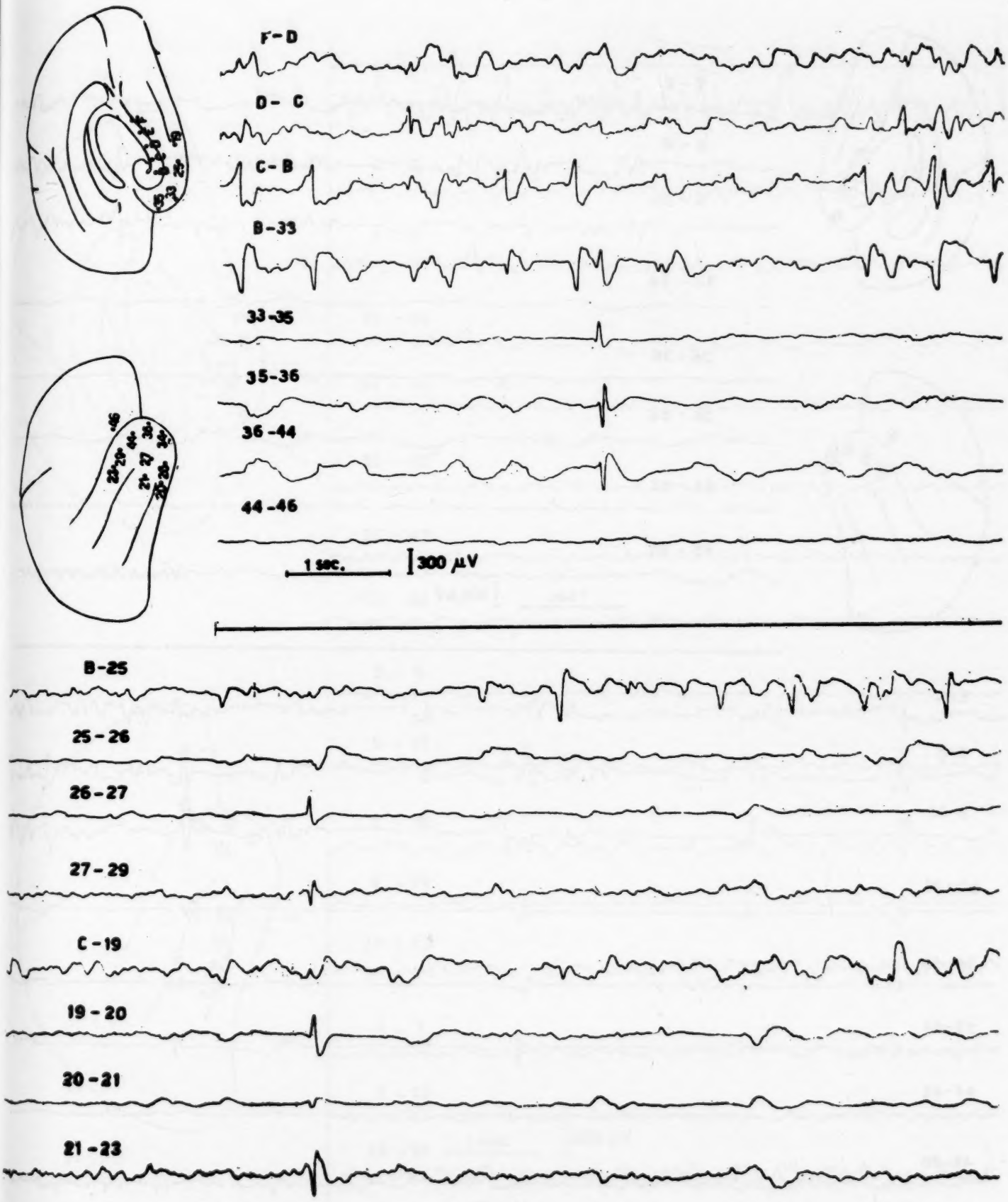


Fig. 7

Right anterior temporal epileptogenic focus; patient awake. Upper tracing; recording from hippocampal gyrus and temporal pole: frequent discharges of spikes and sharp waves from anterior hyppocampal gyrus (electrode B) and random spikes on temporal pole asynchronous with that of the hippocampal gyrus. Lower tracing; transverse leads from hippocampal gyrus to lateral surface: spikes and sharp waves from anterior hippocampal gyrus (electrode B) and asynchronous spikes from lateral surface (electrodes indicated with numbers). Time and amplitude calibration the same for the two records.

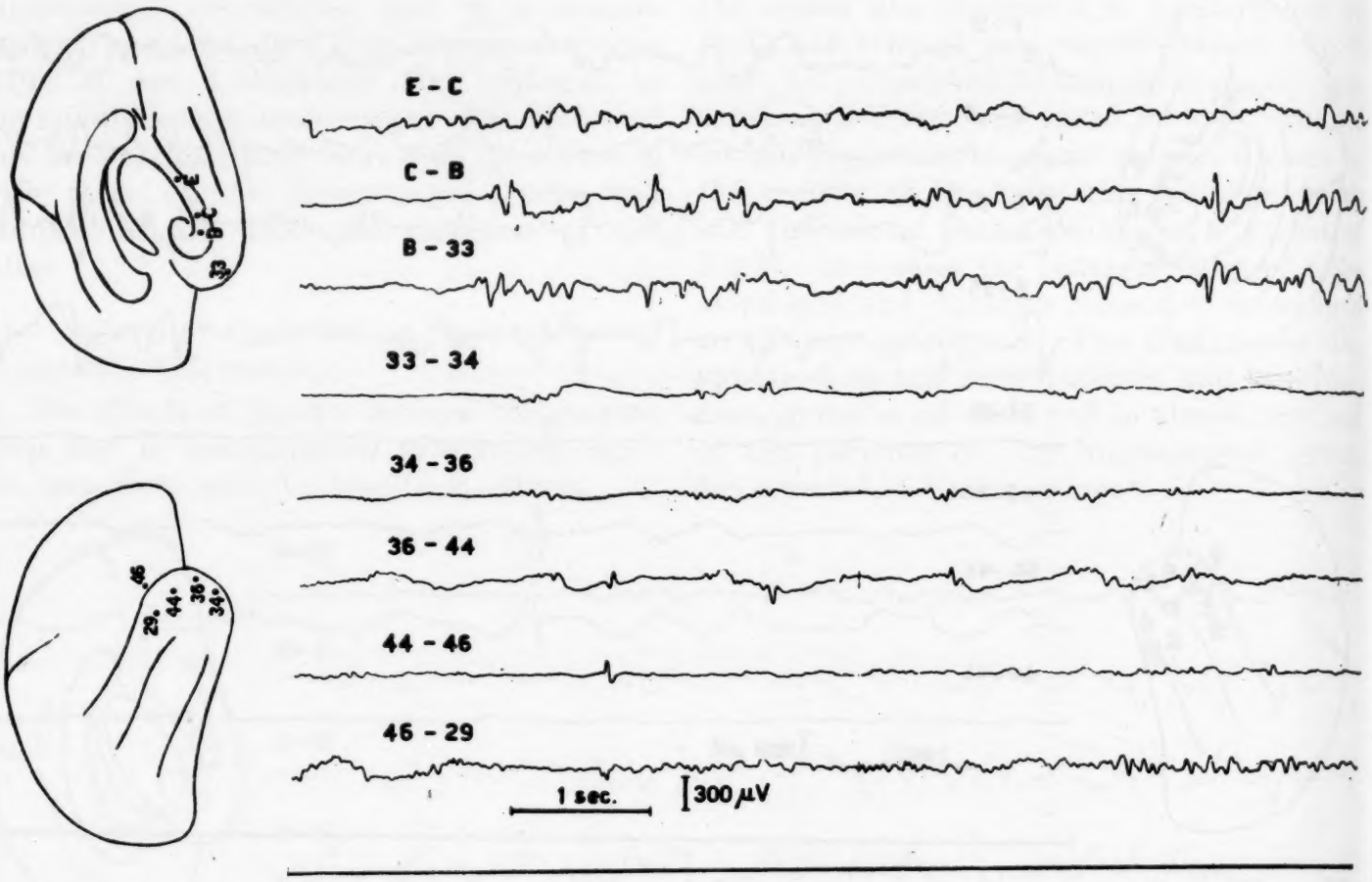
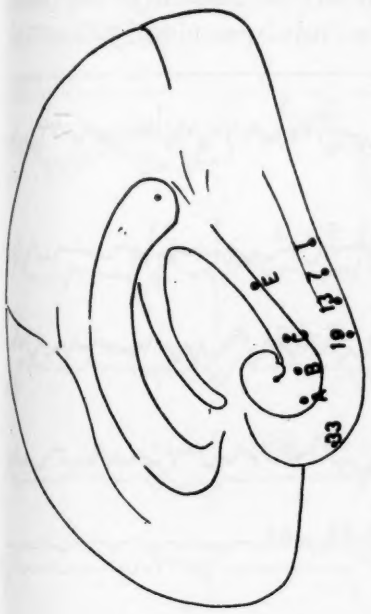
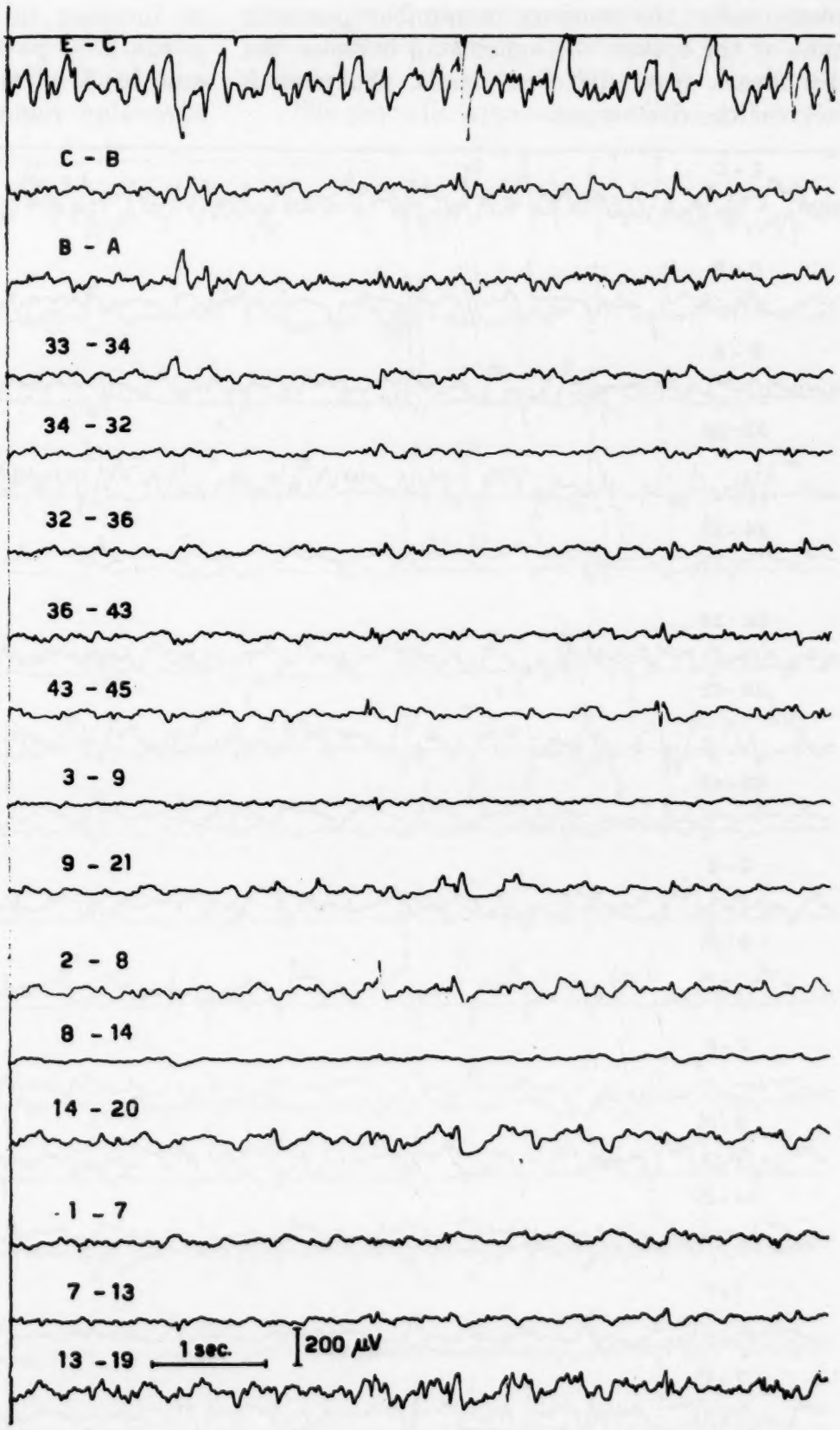


Fig. 8

Same case of the fig. 7, during barbiturate sleep. Upper tracing, 1 min. after the injection of 150 mg. of Pentothal; depression of slow activity and spikes on hippocampal gyrus (electrodes indicated with letters); barbiturate spindles are seen on temporal pole (electrodes indicated with numbers). Lower tracing, 40 sec. after the upper one: synchronous spike discharges on hippocampal gyrus and temporal pole with reciprocal intervals of about 1-2 sec. (Calibration of time and amplitude the same for the two records.)





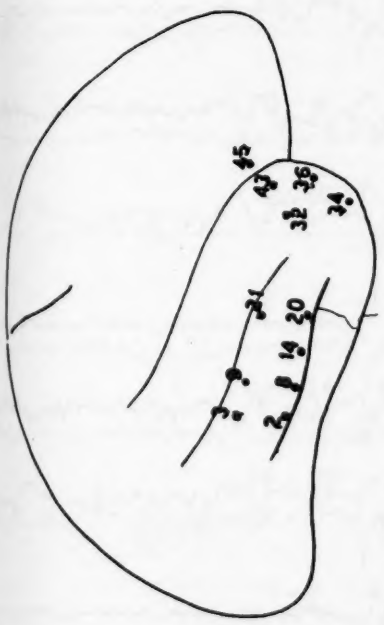


Fig. 9

Right anterior temporal epileptogenic focus; patient awake. Recording from hippocampal gyrus (letters), pole, basal and lateral surface (numbers) of the temporal lobe: hight amplitude spike activity from posterior hippocampal gyrus.

(fig. 8). The main phenomena noted in this phase were: the increase in number per unit time of the spikes, the synchrony between the discharges from different leads, the periodicity of the discharges.

The number of the spikes was observed to increase in 7 cases in the hippocampal gyrus, in 5 patients in the region of the pole and in 2 of these also in the suprasylvian opercular region. In one case only an in-

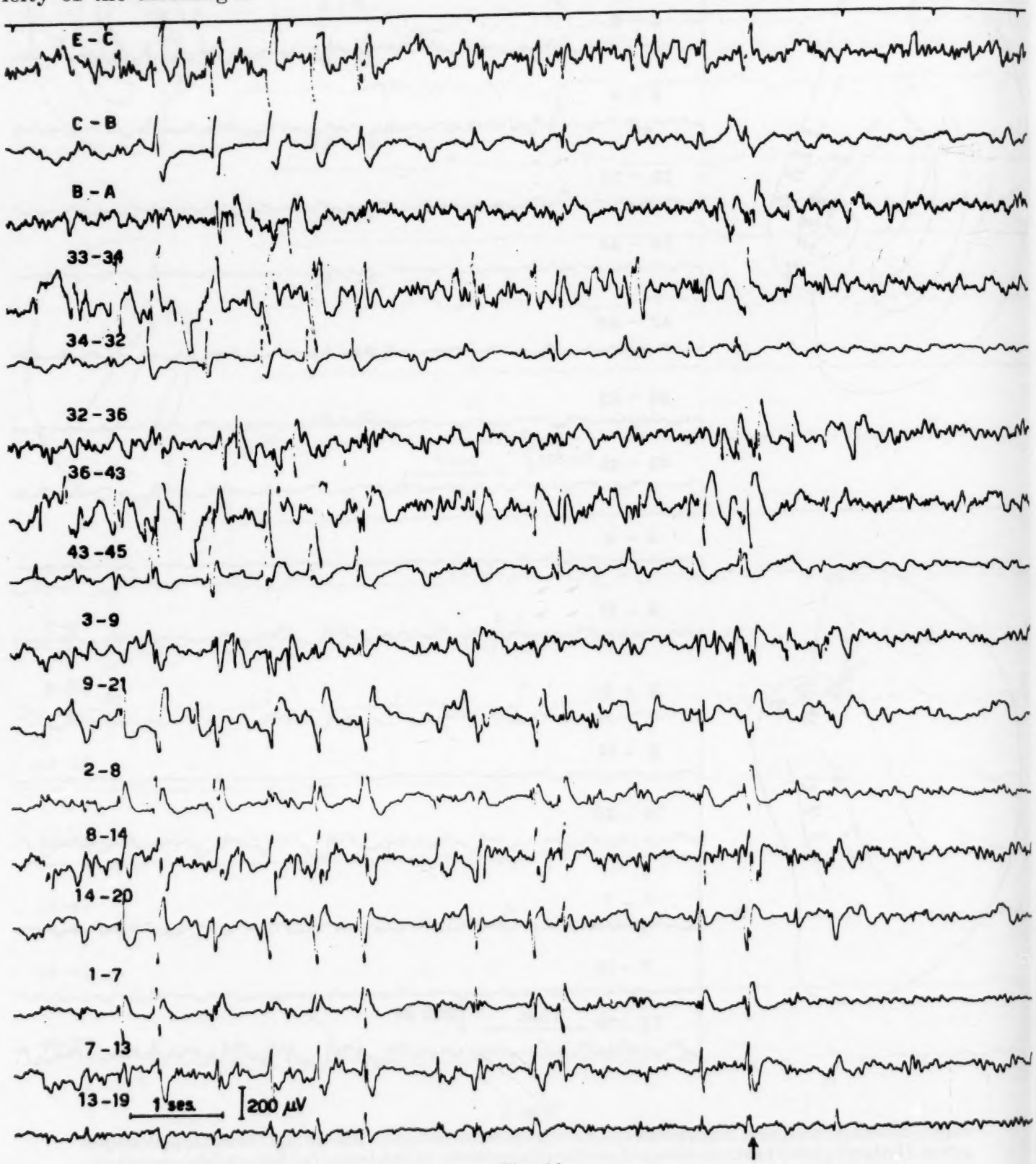


Fig. 10

Same case and same leads of fig. 9 during spontaneous sleep. Synchronous spike discharges on all leads. Inhibition of epileptic activity when the patient is roused (indicated by the arrow).

crease in the number of spikes was observed from the lateral convolutions.

In the same patients in which augmentation of the discharges occurred, the spikes from the pole and lateral convolutions were synchronous with those from the uncinate gyrus. In 2 cases synchronous volleys were also observed during spontaneous sleep (fig. 4 and 10).

The periodic appearance of the spikes was

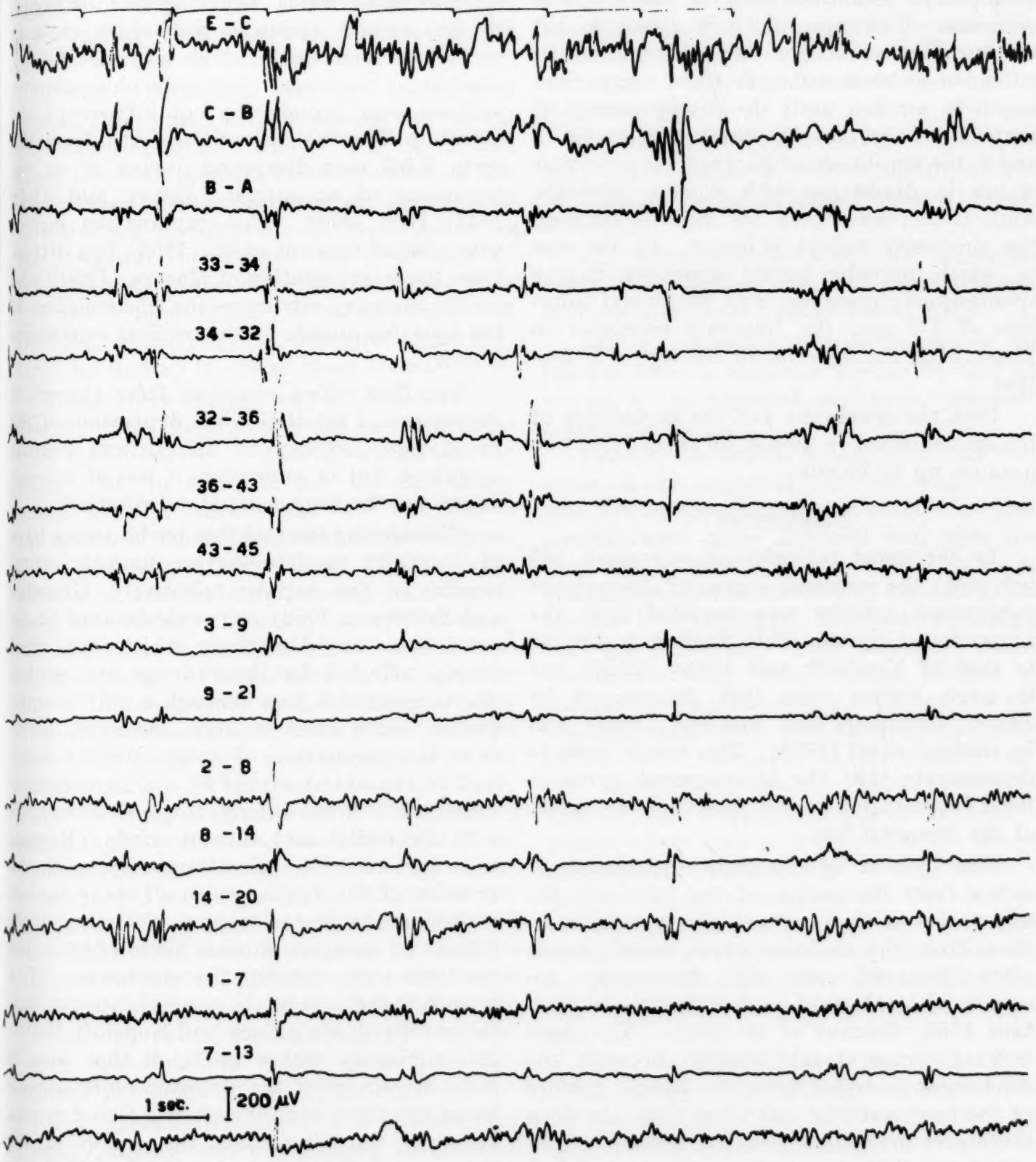


Fig. 11

Same case and same leads of fig. 9 and 10, during barbiturate sleep. Synchronous discharges of spikes of about 1 sec. intervals, simultaneous with barbiturate spindles.

noted in 5 cases simultaneously on both the hippocampal gyrus and the lateral aspect of the lobe, and in two other cases only on the temporal tip. The discharges occurred at relatively regular intervals of 1-3 sec. (fig. 6, 8 and 11). The time interval between two successive discharges was not constant, but the duration was longer during deeper sleep; it tended to become shorter when the patient began to awaken until the disappearance of periodicity. As may be observed from fig. 6 and 8, the amplitude of paroxysmal potentials is less in discharges with shorter intervals, while it increases when the interval between two successive volleys is longer. In one case in which periodic bursts appeared during spontaneous drowsiness with reciprocal intervals of 1-2 sec., the intervals increased to 15 sec. after the injection of 200 mg. of Pentothal.

Both the synchrony and the periodicity of the spikes lasted in almost all cases from two minutes up to 10 min.

DISCUSSION

In the great majority of our cases (89 per cent) the maximal degree of interseizure paroxysmal activity was recorded from the hippocampal gyrus. This finding is similar to that of Kendrick and Gibbs (1957) but is much higher than that determined by Jasper, Pertuisset and Flanigin (1951) and by Gastaut *et al.* (1953). This result tends to demonstrate that the hippocampal gyrus is more frequently involved than the other zones of the temporal lobe.

The lack of synchronous appearance of spikes from the region of the pole and the other areas of the temporal lobe in relation to those from the uncinate gyrus, which we so often observed, was also frequently encountered by Gastaut *et al.* (Paillas and Gastaut 1950; Gastaut *et al.* 1953). The same lack of temporal relationships between the discharges recorded from the lateral surface of the temporal lobe and those from the deep structures were observed by Brazier *et al.* (1954 and 1956) in relation to the amygdaloid region, and by Kellaway (1956) and Kajtor *et al.* (1957) in relation to the hippocampus. Penfield and Jasper (1954) also occasionally noted changes in the characteristics of the form and appearance of the spikes from the anterior and posterior portions of the uncinate gyrus.

Our cases which demonstrate, during a clinical attack, epileptic discharges circumscribed to some areas which may not be accessible to the usual electroencephalographic methods, can explain the not infrequent observation that the epileptic activity from the scalp EEG may disappear during or at the beginning of an attack (Jasper and Daly 1947; Hill 1949). This explanation agrees with that of Gastaut *et al.* (1953) but differs from the interpretation of Mazars (1950) who on the contrary attributes the phenomenon to the small amplitude of the cortical convulsive activity.

The first effect resulting from the rapid injection of Pentothal is the depression of the paroxysmal activity in all cortical regions examined, but in some cases it was of a lesser degree in the hippocampal convolution.

Considering the fact that barbiturates have the capacity to depress the synaptic transmission of the impulses electively (Larabée and Posternak 1952) one could be lead to deduce that the discharges which are most deeply affected by these drugs are evoked discharges which pass through a polysynaptic system. In 8 cases we have observed, moreover, the persistence of spikes strictly localized in the anterior part of the hippocampal convolution even during surgical anesthesia with Pentothal and nitrous oxide (Rovetta and Suriani 1956) simultaneously with depression of the discharges in all other regions including the posterior part of the uncinate gyrus. In epileptic animals too anesthesia has the effect to restrict the discharges of a seizure to the zone of the cortical experimental focus (Ward, McCulloch and Kopeloff 1948): this similarity makes us think that also in some of our cases the primary epileptogenic focus was situated in the cortical firing region. However, in other cases the origin of the paroxysmal discharges remains doubtful.

The slow waves of 6-4 and as low as 2.5 c/sec. of small and medium amplitude ob-

served in our tracings show the character of paroxysmal activity. These appear especially in the regions of the hippocampal gyrus and the temporal pole and tbey are strongly depressed by barbiturates. Apparently they are scantly summated potentials evoked by discharges of deep origin. Chatrian (1953) also made similar observations in this regard and gave a similar explanation.

Besides depression of the paroxysmal activity, we must consider, among the effects of Pentothal, others which occur later and these are: (*a*) increase in the number of the discharges; (*b*) appearance or increase of synchronous discharges in different points on the temporal cortex; (*c*) the possibility of periodic appearance of spike discharges both in a synchronous manner in various regions of the lobe (uncinate gyrus, pole and lateral surface) or limited to one of these areas.

These three effects will be considered together. Most investigators are of the opinion that the occurrence of focal spikes in the scalp EEG in epileptic patients during induced sleep is due to this state and not to the action of the administered drugs (Fuster, Gibbs and Gibbs 1948; Fuster 1951). It has also been observed that during barbiturate sleep occasionally there may be a diffusion of the discharges to the hemisphere contralateral to the focus (Pampiglione and Kerridge 1956). Pampiglione (1953) observed that during electrocorticographic registrations also there was an increase in the spikes after the administration of Pentothal in 5 out of 10 subjects. Recently Kajtor *et al.* (1957) recorded simultaneously from the lateral surface of the temporal lobe and from the ventricular aspect of Ammon's horn through an incision of the second lateral convolution. The authors found that light sleep and drowsiness induced by Evipan intensely activated spike discharges in the hippocampus, while deep sleep increased the paroxysmal activity in the temporal neocortex and at the same time suppressed the spikes in the hippocampus.

The periodic character of the spike discharges during barbiturate sleep in cases of temporal lobe epilepsy observed by us resembles, in some respect, the bursts of cortical potentials evoked by afferent stimuli or by application of strychnine on the cortex of anesthetized cats and in "encéphale isolé" preparations (Moruzzi *et al.* 1950). It is suggested that this periodicity is due to cyclic modifications of the neural excitability, commonly observed in some phases of the sleep, in relation to the elimination of the ascending influence of the brain stem reticular activating system. This hypothesis is based on the following facts:

(1) the intermittent epileptic spikes appear in that phase of induced sleep in which the appearance of spindle bursts is usually observed;

(2) simultaneous with the convulsive spikes there appear trains of rapid waves of medium amplitude strictly due to sleep;

(3) the intervals between successive discharges have a duration similar to that observed in experimental conditions (generally from 1 to 3 sec.).

Because the ECoGs where taken only from areas of one temporal lobe, one could think that the described changes of barbiturate sleep records were more diffused and also that they for a great part, could be made of spontaneous potentials of deep narcosis (spontaneous K complexes). However, we showed that the paroxysmal spike potentials during barbiturate sleep were similar to that recorded during spontaneous sleep and the only contamination of the records were the spindle bursts which occurred simultaneously with the epileptiform spikes. This paroxysmal activity was observed in phases of light or medium deep sleep as is proved by the clinical state of the patients, by the presence of spindles in the records and by the short intervals between bursts. On the other hand the doses of Pentothal were equal to that used for preoperative EEG in which the discharges were confined, during sleep, to the temporal lobe.

We also observed that the intervals between the periodic discharges decreased with the diminishing of the barbiturate effect and that the amplitude of the spikes of each discharge was higher or lower (fig. 6 and 8) according to the lenght of the reciprocal in-

tervals. This last phenomenon makes us suppose that at equal levels of anesthesia there is an optimum lapse of time between the discharges so that the epileptic potential acquires its greatest amplitude as is suggested by Gastaut *et al.* (1951) on the variations of cyclic excitability of the central nervous system under the influence of depressive substances. Recent researches of Brookhart and Zanchetti (see Zanchetti 1957) show, however, that the amplitude of the pyramidal responses to cortically applied stimuli during sleep spindles, changes according to the phase of the spindle potential at which the stimulus is induced.

The so-called epileptic sleep activation, characterized by the increase of seizure discharges, by their higher degree of synchrony and by their periodicity, may be considered therefore to be due to the effect of cyclic variations of the neuronic cortical and subcortical excitability.

Also the concept of Brazier (1955) on the disruption during sleep of a homeostatic regulation on the convulsive activity as cause of the increase of the spike discharges, may be taken into account. According to this concept, sleep would abolish the autoregulative activity of a cortico-reticulo-cortical system which in turn is activated by the same cortical discharges.

The hypothesis of Fuster (1953), who considers the phenomenon of sleep facilitation as a result of the synchrony of the cortical activity, is not definitively in contrast with our concept. In fact if the cortical effect of sleep is considered as part of a general modification of the basic excitability of the brain, and not as an individual peculiarity of the cortex, the difference between the Fuster's hypothesis and our own is more appearant than real.

SUMMARY

1. In 18 cases of temporal lobe epilepsy electrocorticographic examinations were made with indwelling electrodes on the surface of the whole temporal lobe, which were left in place from 24 to 48 hours. Records were made with patients awake, under light or medium-deep barbiturate sleep and during surgical anesthesia.

2. At rest, maximum seizure activity was recorded in the majority of the cases (89 per cent) from the hippocampal gyrus and especially from its anterior part. Paroxysmal activity occurred also in other areas of the temporal lobe, especially in the pole, but generally it was less marked than in the hippocampal gyrus. Asynchronism between the discharges from the uncinate gyrus and the other temporal regions was commonly observed.

3. The effects of rapidly induced barbiturate sleep consist in an early depression of the convulsive activity followed by an increase in the appearance of spikes and by their synchronous diffusion to different areas of the lobe. These discharges may appear as relatively periodical bursts.

4. Changes in the convulsive activity during sleep, commonly called "activation", are discussed.

RÉSUMÉ

1. Chez 18 cas d'épilepsie du lobe temporal des examens électrocorticographiques furent réalisés par des électrodes implantées sur la surface de tout le lobe temporal et laissées sur place de 24 à 48 heures. Des enregistrements étaient pratiqués avec les malades éveillés ou en sommeil barbiturique léger ou modérément profond, et sous l'effet d'anesthésie chirurgicale.

2. Au repos l'activité critique maxima était enregistrée dans la majorité des cas (89 pour cent) dans la circonvolution de l'hippocampe, plus particulièrement dans sa partie antérieure. L'activité paroxystique se voyait aussi dans d'autres régions du lobe temporal, en particulier le pole, mais, en général, elle était moins marquée que dans la région de la circonvolution de l'hippocampe. Il était courant d'observer de l'asynchronisme entre les décharges de l'uncus de l'hippocampe et des autres régions temporales.

3. Les effets du sommeil barbiturique léger ou modérément profond, rapidement

induit, consistent en une dépression précoce de l'activité convulsivante, suivie d'une augmentation dans l'apparition des pointes et par leur diffusion synchrone à des régions différentes du lobe. Ces décharges peuvent paraître sous forme de bouffées relativement périodique.

4. On discute les altérations de l'activité convulsivante pendant le sommeil, appelées couramment « activation ».

ZUSAMMENFASSUNG

1. In 18 Fällen von Schläfenlappenepilepsie wurden elektrokortikographische Untersuchungen mit implantierten Elektroden ausgeführt. Die Elektroden waren über die ganze Oberfläche des Schläfenlappens verteilt und wurden für 24 bis 48 Stunden *in situ* gelassen. Das Hirnstrombild wurde sowohl am wachen Patienten aufgenommen als auch unter leichtem oder mitteltiefem Barbituratschlaf und unter chirurgischer Vollnarkose.

2. Im Ruhezustand wurde in der Mehrheit der Fälle (89 Prozent) das Maximum der Krampfaktivität im Gyrus hippocampi und speziell in seinem vordersten Abschnitt aufgezeichnet. Paroxysmale Aktivität ereignete sich auch in anderen Arealen des Schläfenlappens, speziell im Temporalpol, aber im allgemeinen war die Aktivität dort weniger hervorstechend als im Gyrus hippocampi. Ein Fehlen von Synchronisierung der Entladungen zwischen Gyrus hippocampi und anderen Regionen des Schläfenlappens war eine häufige Beobachtung.

3. Der Effekt von rasch induziertem, leichtem oder mitteltiefem Barbituratschlaf bestand in einer frühen Depression der Krampfaktivität, welche von einer erneuten Zunahme im Auftreten von Spitzenentladungen, gefolgt wurde, wobei diese sich in synchroner Weise über verschiedene Gegenden des Schläfenlappens verteilten. Diese Entladungen erschienen manchmal in der Form von ziemlich periodischen, gruppierten Potentialen.

4. Gewisse im allgemeinen als Aktivierung bezeichnete Veränderungen der Krampfaktivität im Schlaf werden besprochen.

REFERENCES

AMADOR, L. V. Surgical aspects of temporal lobectomy in man. *Arch. Neurol. Psychiat.*, Chicago, **1955**, *74*: 567.

BAILEY, P. Betrachtungen über die chirurgische Behandlung der psychomotorischen Epilepsie. *Ztbl. Neurochir.*, **1954**, *14*: 195-206.

BAILEY, P. and GIBBS, F. A. The surgical treatment of psychomotor epilepsy. *J.A.M.A.*, **1951**, *145*: 365-370.

BERGAMINI, V., MAROSSERO, F. e MASPES, P. E. L'attivazione con Cardiazol locale in elettrocorticografia. *Riv. Neurol.*, **1953**, *23*: 434-446.

BRAZIER, M. A. B. Neuronal structure, brain potentials and epileptic discharge. *Epilepsia*, **1955**, *4*: 9-18.

BRAZIER, M. A. B. Depth recording from the amygdaloid region in patients with temporal lobe epilepsy. *EEG Clin. Neurophysiol.*, **1956**, *8*: 532-533.

BRAZIER, M. A. B., SCHROEDER, H., CHAPMAN, W. P., GEIGER, C., FAGER, C., POPPEN, J. L., SALOMON, H. C. and YAKOVLEV, P. I. Electroencephalographic recordings from depth electrodes implanted in the amygdaloid region in man. *EEG Clin. Neurophysiol.*, **1954**, *6*: 702.

BROGLIA, S., MAROSSERO, F. e MASPES, P. E. Foci temporali posteriori e temporo-parietali: considerazioni cliniche, elettroencefalografiche, elettrocorticografiche ed anatomo-chirurgiche. *Riv. Neurol.*, **1954**, *24*: 738-748.

CHATRIAN, G. E. Etude électroencéphalographique et électrocorticographique du rythme thêta local dans les épilepsies temporales. *Rev. Neurol.*, **1953**, *88*: 384-386.

DELL, M. B. L'épilepsie temporale. *Presse méd.*, **1953**, *1*: 505-508.

FALCONER, M. A., HILL, D., MEYER, A., MITCHELL, W., POND, D. A., HOARE, R. D. and PAMPIGLIONE, G. Treatment of temporal lobe epilepsy by temporal lobectomy. *Lancet*, **1955**, pp. 827-835.

FUSTER, B. Efecto del sueño inducido con diferentes drogas, sedantes, hipnóticos y anticonvulsivantes sobre el electroencefalograma en la epilepsia psicomotriz. *Arch. Urug. Med. Cir.*, **1951**, *39*: 245-270.

FUSTER, B. EEG activation under natural or induced sleep. *EEG Clin. Neurophysiol.*, **1953**, Suppl. *4*: 108-120.

FUSTER, B., GIBBS, E. L. and GIBBS, F. A. Pentothal sleep as an aid to the diagnosis and localization of seizure discharges of the psychomotor type. *Dis. Nerv. Syst.*, **1948**, *9*: 199-202.

GASTAUT, H. Le lobe temporale on O-N-O. Etude électroencéphalographique. *Rev. Oto-Neuro-Opht.*, **1950**, *22*: 301-328.

GASTAUT, H., NAQUET, R., VIGOUROUX, R., ROGER, A. et BADIER, M. Etude électrographique chez l'homme et chez l'animal des décharges épileptiques dites ''psychomotrices''. *Rev. Neurol.*, **1953**, *88*: 310-354.

GASTAUT, H. et Y., ROGER, A., CORRIOL, G. et NAQUET, R. Etude électrographique du cycle d'excitabilité corticale. *EEG Clin. Neurophysiol.*, **1951**, *3*: 401-428.

GREEN, J. R., DUISBERG, R. E. H. and MCGRATH, W. B. Electrocorticography in psychomotor epilepsy. *EEG Clin. Neurophysiol.*, **1951**, *3*: 293-299.

GUILLAUME, J. et MAZARS, G. Cinq cas de foyers épileptogènes insulaires opérés. *Rev. Neurol.*, **1948**, *81*: 766-771.

GUILLAUME, J., MAZARS, G. et MAZARS, Y. Indications chirurgicales dans les épilepsies dites ''temporales''. *Rev. Neurol.*, **1953**, *88*: 461-501.

HILL, D. The electroencephalographic concept of psychomotor epilepsy; a summary. *IV. Congr. Neurol. Intern.*, Vol. 1, Masson et Cie., Paris, **1949**.

JASPER, H. and DALY, D. Suppression of electroencephalogram during the onset of an epileptic seizure. *Proc. Amer. Soc. EEG*, **1947**, p. 242.

JASPER, H. and KERSHMAN, J. Electroencephalographic classification of the epilepsies. *Arch. Neurol. Psychiat.*, Chicago, *45*: 903-943.

JASPER, H., PERTUISSET, B. and FLANIGIN, H. EEG and cortical electrogram in patients with temporal lobe seizures. *Arch. Neurol. Psychiat.*, Chicago, *51*: 272-290.

KAADA, B. R. Temporal lobe seizures. *EEG Clin. Neurophysiol.*, **1953**, Suppl. *4*: 235-246.

KAJTOR, F., HULLAY, J., FARAGO, L. and HABERLAND, K. Effect of barbiturate sleep on the electrical activity of the hippocampus of patients with temporal lobe epilepsy. *EEG Clin. Neurophysiol.*, **1957**, *9*: 441-451.

KELLAWAY, P. Depth recording in focal epilepsy. *EEG Clin. Neurophysiol.*, **1956**. *8*: 527-528.

KENDRICK, J. F. and GIBBS, F. A. Origin, spread and neurosurgical treatment of the psychomotor type of seizure discharge. *J. Neurosurg.*, **1957**, *14*: 270-284.

KRAYENBÜHL, H., HESS, R. und WEBER, G. Elektroenzephalographische und therapeutische Ergebnisse der Behandlung von 21 Fällen mit sogenannten Temporallappen-Epilepsien. *Ztbl. Neurochir.*, **1954**, *14*: 206-211.

LARRABÉE, M. G. and POSTERNAK, J. Selective action of anesthetics on synapses and axons in mammalian sympathetic ganglia. *J. Neurophysiol.*, **1952**, *15*: 91-114.

LENNOX, M. and BRODY, B. S. Paroxysmal slow waves in the EEG of patients with epilepsy and with subcortical lesions. *J. nerv. ment. Dis.*, **1946**, *104*: 237-248.

LIDDEL, D. W. and CORSELLIS, J. A. N. Clinical-pathological findings in epilepsy with special reference to the temporal lobes. *Intern. Congr. Neuropat.*, London, Sept. **1955** (reprint).

MARSHALL, C. Flexible subdural electrodes for corticography. *EEG Clin. Neurophysiol.*, **1953**, suppl. *3*: 36.

MASPES, P. E., GRATTAROLA, F. R. et MAROSSERO, F. Etude anatomopathologique de 36 cas d'épilepsie temporale opérés. *Acta Neurol. Psychiat. Belg.*, **1956**, *56*: 103-114.

MASPES, P. E. e MAROSSERO, F. L'epilessia temporale ed il suo trattamento chirurgico. *Chirurgia*, **1954**, *9*: 171-217.

MAZARS, G. Interprétation du phénomène d'extinction dans la phase initiale des crises focales corticales. *EEG Clin. Neurophysiol.*, **1950**, *2*: 343.

MILLETTI, M. A technique for continuous recording of brain potentials directly from the cortex. *Acta Neurochir.*, **1955**, *4*: 470-472.

MILLETTI, M. A new technique for corticography by means of indwelling electrodes in cases of focal epilepsy. *Arch. Aeurop. Neurochir.*, **1959** (in print).

MORUZZI, G., BROOKHART, J. M., NIEMER, W. T. and MAGOUN, H. W. Augmentation of evoked electrocortical activity during spindle bursts. *EEG Clin. Neurophysiol.*, **1950**, *2*: 29-31.

PAILLAS, J. E. et GASTAUT, H. Documents neurochirurgicaux et électrographiques pour servir à l'étude de l'épilepsie temporale. *Rev. Neurol.*, **1950**, *83*: 393-396.

PAILLAS, J. E., GASTAUT, H., BONNAL, J. et VIGOUROUX, R. Corrélations anatomo-électriques dans l'épilepsie temporale à propos des résultats obtenus chez 38 opérés. *Rev. Neurol.*, **1953**, *88*: 568-574.

PAILLAS, J. E., VIGOUROUX, R., CORRIOL, J. et BONNAL, J. Intérêt de l'enregistrement électrographique du noyau amygdalien au cours des opérations pour épilepsie temporale. *Rev. Neurol.*, **1952**, *86*: 354.

PAMPIGLIONE, G. So-called ''psychomotor'' and ''temporal epilepsy''. Discussion. *Epilepsia*, **1953**, *2*: 91-94.

PAMPIGLIONE, G. and KERRIDGE, J. EEG abnormalities from the temporal lobe studied with sphenoidal electrodes. *J. Neurol., Neurosurg. Psychiat.*, **1956**, *19*: 117-129.

PENFIELD, W. and FLANIGIN, H. Surgical therapy of temporal lobe seizure. *Arch. Neurol. Psychiat.*, Chicago, **1950**, *64*: 491-500.

PENFIELD, W. and JASPER, H. *Epilepsy and the Functional Anatomy of the Human Brain.* Boston, Little, Brown & Co., **1954**.

PETIT-DUTAILLIS, D., CHRISTOPHE, J., PERTUISET, B. et DREYFUS-BRISAC, C. Indications et résultats de l'excision corticale dans l'épilepsie temporale (d'après 20 cas opérés). *Sem. Hôp.*, Paris, **1953**, *29*: 3838-3847.

ROVETTA, P. e SURIANI, U. Effetti degli anestetici generali sulle onde cerebrali accessuali di soggetti epilettici. Analisi elettrocorticografica. *Arch. Neurochir.*, **1956**, *3*: 215-222.

VALLADARES, H. y MARKOVICH, S. Tratamiento quirúrgico y corticografía de las epilepsias psicomotoras. *Neurocirugía*, **1954**, *10*: 167-178.

ZANCHETTI, A. Meccanismi intracorticali della reazione elettroencefalografica di risveglio. In: Problemi di fisiologia e clinica dei sistemi a proiezione diffusa dell'Encefalo. *Atti del Convegno di Parma*, nov. **1957**, Ed. Maccari, Parma.

Reference: ROVETTA, P. Electrocorticographic changes in temporal lobe epilepsy at rest and during induced sleep. *EEG Clin. Neurophysiol.*, **1959**, *11*: 521-538.

PRINTED IN CANADA

ANALYSIS OF CEREBRAL RESPONSES TO FLICKER IN PATIENTS COMPLAINING OF EPISODIC HEADACHE

F. L. Golla, M.D. and A. L. Winter
Burden Neurological Institute, Bristol, England

(Received for publication: May 7, 1958)

INTRODUCTION

Observation of routine clinical recording during photic stimulation led to an impression that a large proportion of subjects who responded predominantly at high stimulus frequencies with a simple form of response (i.e. a fundamental and harmonic "following" response (Walter and Walter 1949) as opposed to subharmonic and paroxysmal discharges), were those complaining of headache. The literature showed no specific investigation of the relationship between headache and flicker response though Ulett (1953) and Shagass (1954) made studies of flicker responses and their association with anxiety states. Subsidiary material of other studies suggested a possible correlation and the observation of Mundy-Castle (1953) may be relevant; he mentions that "European adults describing episodic behaviour disturbances, migraine and headaches" showed considerably greater mean response amplitudes to photic stimulation over the range of 8 to 26 f/sec. than all the other types of cases studied in his survey. The apparent association between a complaint of headache and an extended flicker response prompted further investigation into the details of the evoked activity and the clinical state of the patients, particularly those considered to be suffering from headaches of the migrainous type.

METHOD

The light source was a Scophony electronic stroboscope, giving flashes of blue-white xenon light with a time constant of 15 μsec. The frequency could be varied from 3.5 to 25 flashes per sec. without change in duration or brilliance and to 100 f/sec. at a reduced intensity. The peak intensity of the flash was about 88,000 candles. An improved wave analyser Walter Mark II was used in all investigations. The technique of stimulation was simplified as much as possible in order to ensure uniformity of conditions, economy of time and clarity of statistical analysis. The lamp was stationed about 5 cm. from the subject's nose so that the whole visual field would be illuminated.

Preliminary trials suggested that a repetitive flash rate range of 6 to 24 f/sec. would be sufficient in the great majority of cases. Each flash rate was given for a 10 sec. period. Beginning at 6 f/sec. the flash rate was increased after 10 sec. by 2 f/sec. to 8 f/sec., which was maintained for another period of 10 sec., after which it was increased by another step of 2 f/sec. and so on until the whole range was covered in ten steps. This provided continuous stimulation throughout the range and a full epoch of analysis at each rate.

In some of the preliminary studies it was noticed that short periods of stimulation were liable to evoke a large response for a second or two, which then declined to a very low level. A similar effect is found in certain types of epileptic patient where abnormal discharges may be evoked only at the onset of sudden stimuli. It is likely that mechanisms of sensory adaptation and central habituation come into play with "surprise" stimulation and for the purpose of this particular experiment they would be confusing. The method of continuous stimulation with unobtrusive frequency was used as a compromise to cover the range of frequencies without introducing the provocative effect of sudden changes of rate (fig. 1).

The stepping of the flash rates was done by hand in the preliminary trials, but a "step frequency" switch, designed by Mr. W. Warren, was incorporated in the wave analyser for later studies. The circuit (fig. 2) is a

blocking oscillator with a selector switch (SI) in the grid circuit. This switch progressively changes the resistance of the grid time-constant, hence the frequency of oscillation. The energising coil (CI) of the selector switch receives its energising pulse from the 50 μF capacitor via a pair of contacts (S2) on the epoch change-over switch in the analyser, thus changing the frequency of oscillation of the blocking oscillator every 10 sec. This "step frequency" switch has two main advantages: (1) each flash rate is presented for exactly 10 sec. by the operation of the analyser change-over switch and each flicker period is thus coincident with an analyser epoch and, (2) the flash rate of each flicker period can be set to exactly that of its corresponding resonator in the analyser.

The setting is achieved quite easily in the following way: it is customary to monitor the stimulus by recording the output of a barrier layer selenium cell placed in the path of the light, on one channel of the EEG recorder. If the monitor channel is now analysed the frequency of the stimulus will be shown by the analyser. Each stimulus frequency may now be adjusted by means of its appropriate control on the "step frequency" switch to match the frequency of the respective analyser resonator. There is one control for each frequency, i.e. one control for 6 f/sec., one for 8 f/sec. and so on to 24 f/sec., and each of

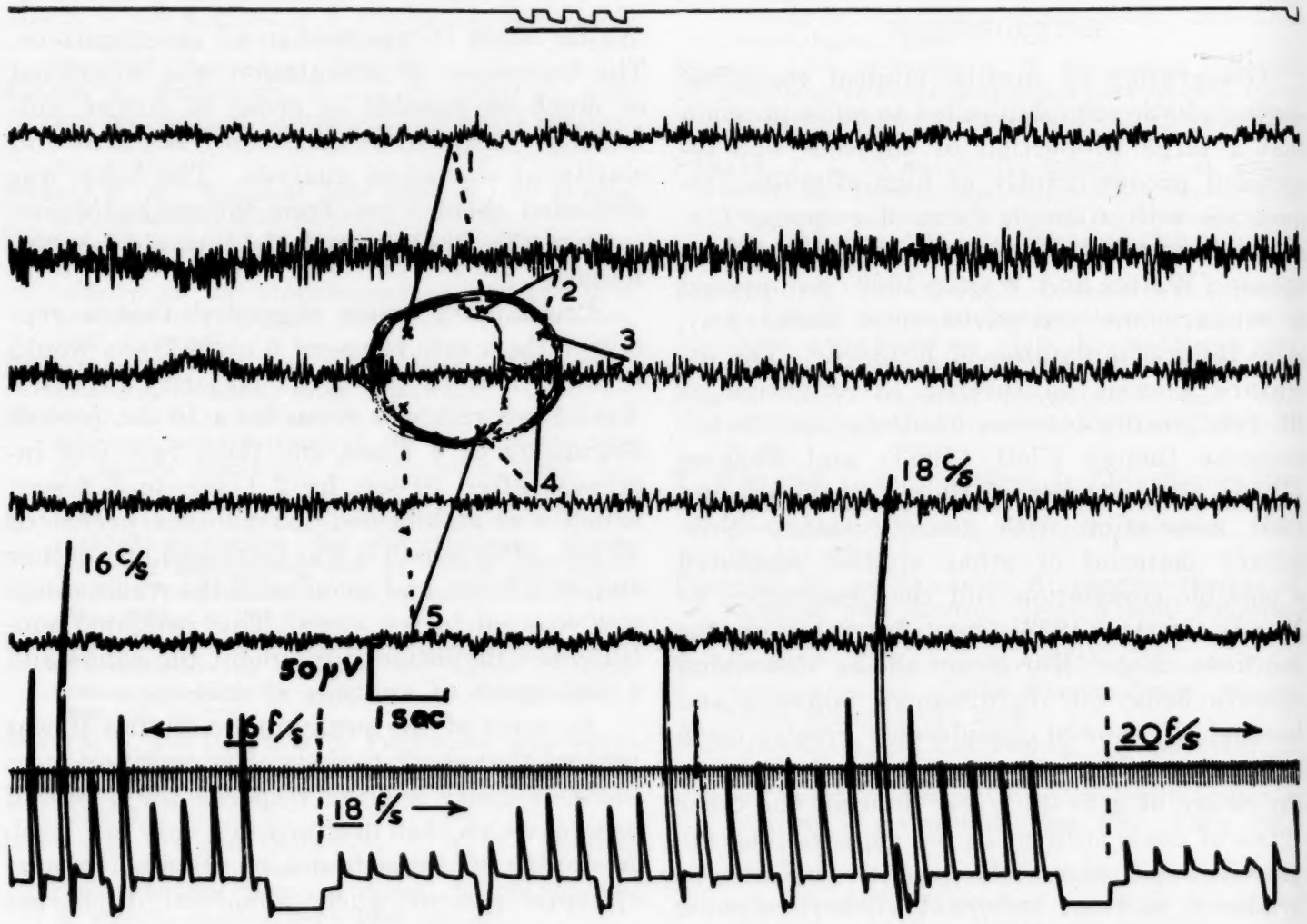


Fig. 1

A record of a typical "following" response to photic stimulation with analysis of channel 4. The response to 16 f/sec. can be seen in the last part of the epoch shown in the left of the figure, while the complete epoch shows the response to 18 f/sec. The paper speed is 1.5 cm/sec. and although the primary response is perhaps a little difficult to see at this speed the analysis is more easily read than at higher paper speeds. N.B. No break in the stimulation can be observed during the change from 16 to 18 f/sec. between the two epochs.

these controls is set in turn to give the maximum response as measured by the analyser. For example, with the "step frequency" switch at 6 f/sec. and the monitor channel being analysed, the 6 f/sec. frequency control on the "step frequency" switch is adjusted to give a maximum deflection at 6 c/sec. as indicated by the analyser with the 5 and 7 c/sec. responses of the analyser evenly proportioned on each side; the 6 f/sec. stimulus is then known to be tuned to exactly the same frequency as the 6 c/sec. resonator of the

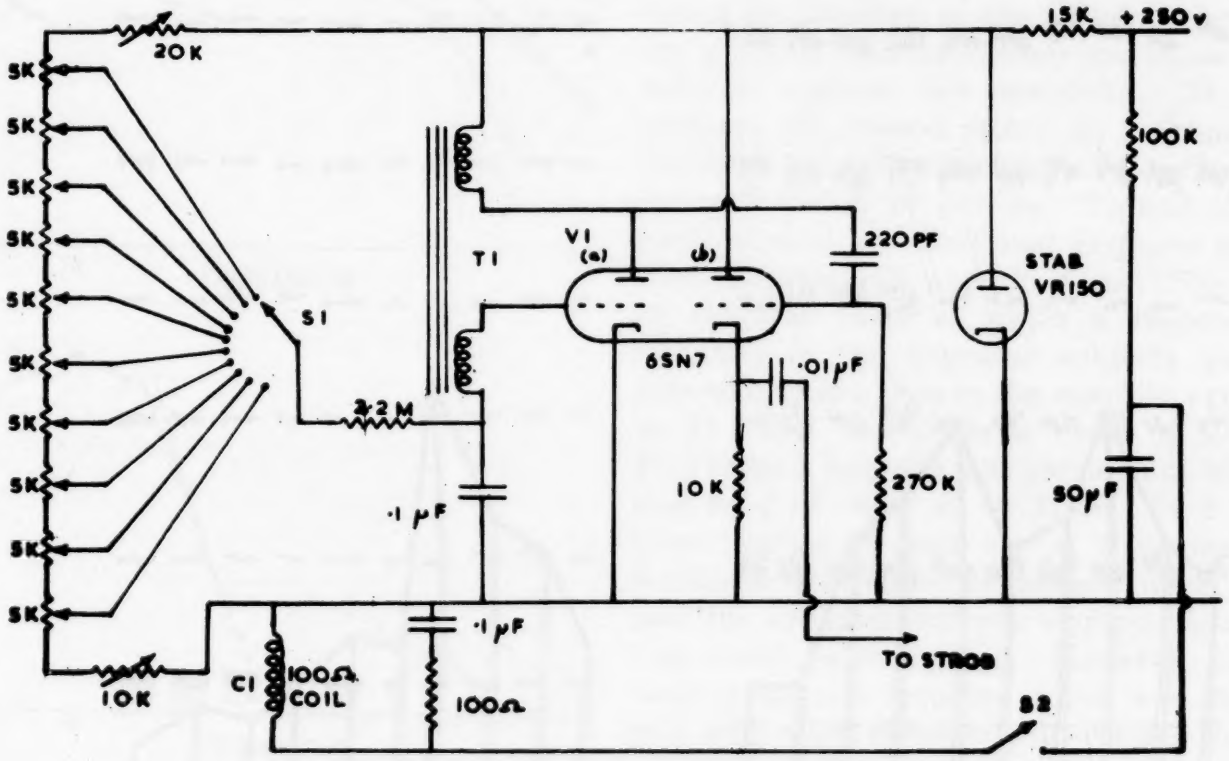


Fig. 2

The circuit of the stepped flash frequency generator. Switch S1, CI is operated from the change-over contacts S2 which are in the frequency analyser, at the end of each epoch. The 5K controls are adjusted so that the flash frequencies match those of the analyser.

analyser. This procedure ensures a constant and strict correspondence of frequency between the stimulating and recording devices.

Prior to photic stimulation in each case the gain of the analyser was adjusted so as just to indicate the mean level of the spontaneous components in the EEG over the frequency range concerned. Since stimulation was performed with the eyes closed, this adjustment often resulted in the alpha components being represented by full scale analyser deflections. This does not interfere with analysis of the evoked responses since the stimulation generally reduced the amplitude of the alpha activity. The evoked responses are often smaller in amplitude than the mean level of intrinsic activity and it is necessary to set the analyser gain high enough to provide measureable deflections over the whole range of stimulus frequencies. In this way, full advantage can be taken of the resolution of the frequency analyser, which permits accurate measurement of the abundance of components at steady frequencies even when these are masked by larger components in the primary records. In many of the cases in this series the evoked response could not be identified at all in the primary records, even when these were taken at a high paper speed, and in none of them could the response be measured without analysis. The term *abundance* is used to describe the amplitude of the analyser deflections (Walter and Shipton 1957); these have the dimensions of signal amplitude, duration and frequency but it seems desirable at this stage to avoid the explicit terms "energy" and "power" and the ambiguous ones "activity" and "intensity".

In each case a short preliminary trial of the effect of flicker was made to discover which hemisphere gave the greater response and the analyser was then switched to the temporo-occipital channel on that side. Preliminary observations did not disclose any significant relation between the laterality of the response and that of the headache or other complaint. The automatic stepping switch was then set to initiate and the sequence of flicker frequencies was gone through.

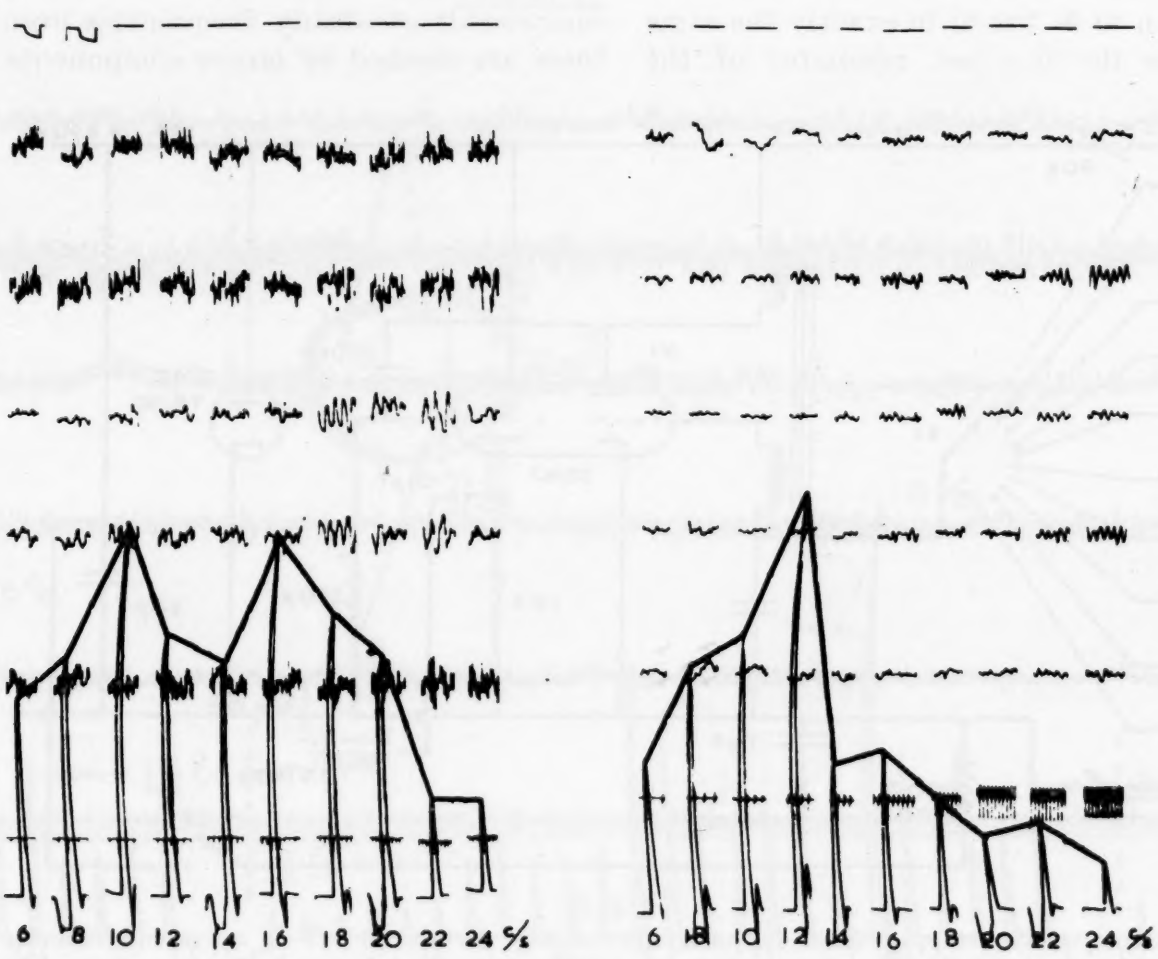


Fig. 3

Two sets of analyses composed of ten epochs of analysis in each case. The one on the left is from a subject with a migrainous headache and the one on the right a control subject. The histograms obtained in this way form the raw measure from which the normalised curves are drawn.

The final result was a set of ten epochs of analysis; each epoch contained the spectrum of intrinsic activity together with that of the response evoked by the corresponding flicker. In each of these epochs only the abundance at the fundamental stimulus frequency was considered. There were therefore only ten simple measurements to be made for each subject (fig. 3). These measurements taken together provide the flicker response spectrum for each patient as a histogram and can be plotted as a simple graph of abundance against frequency. This curve does not however facilitate comparison between patients since the absolute levels vary from subject to subject because of intrinsic differences and adjustments of analyser gain. To make the curves from different patients comparable, they were "normalised" by multiplying each ordinate by a factor to bring the maximum abundance in the alpha band to a figure of 100 arbitrary units (fig. 4).

There is no particular theoretical justification for using the peak abundance in the alpha band as a datum mark, but empirically this

procedure seems to give the clearest distinction between response characters in the clinical groups here considered.

SUBJECT MATERIAL

As a control population, 50 subjects with no complaint of headache were examined by the above method. Of these, 35 were normal people in the sense that they had never sought advice for a neuro-psychiatric ailment, and 15 were epileptic patients.

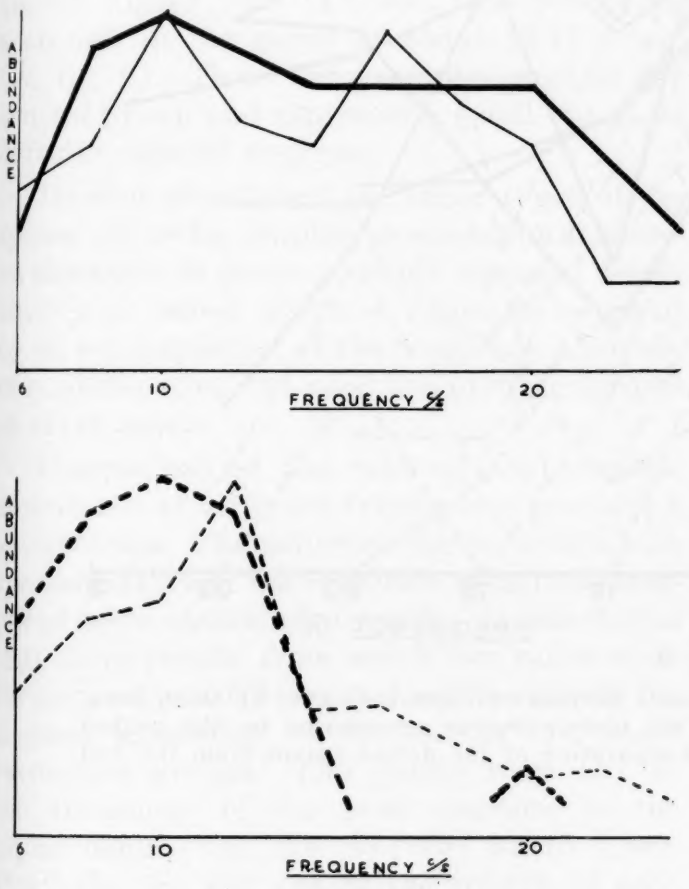


Fig. 4

The full lines in the top figures are normalised response curve of subjects with migraine. The thick one represents the mean of a number of such curves and the thin one is the normalised curve of the migraine subject shown in figure 3.
The thick broken line in the bottom figure is the mean of a number of normalised curves of normal subjects and the thin broken line is of the normal subject in figure 3.

One hundred and fifteen patients complaining of headache were examined, some many times, in the same way as the control group. These patients were drawn from the outpatient clinic of the Burden Neurological Institute. All were suffering from episodic severe headaches, associated with one or more of the following symptoms: (1) nausea with or without vomiting, (2) visual disturbances, (3) paraesthesia. In some cases, no aetiological factor could be found. One could call these cases idiopathic migraine. In others the headaches followed head injury or were associated with epilepsy and could therefore be called symptomatic.

RESULTS

A striking difference was observed between the analysis of the flicker responses of the patients with headaches and those of the subjects without this complaint. Of the 50 controls, 42 showed either no response or a fundamental following response to flash rates between 6 and 14 per sec. Two of these 42 cases showed an additional response to flash rates between 16 and 20 f/sec. The range of stimulus rates at which a response was obtained in the migraine subjects was considerably wider than in the controls, extending to 18 f/sec. and in some cases to 30 f/sec. In 5 cases a response was obtained at 45 f/sec. and in 2 of these at 60 f/sec. In 3 of the cases during at least one of their many recordings, myoclonic discharges were evoked and the examination was stopped before the test could be completed. However, in 2 of these 3 cases a response curve was obtained at a time when myoclonic discharges were not evoked and these were included in the results. Typical response curves of a control subject and a migrainous headache subject are shown in figures 3 and 4.

By superimposing an equal number of both types of curves, the mean difference between them could be discerned by inspection. As explained above, the shape and relative proportions of the response curves are emphasised at the expense of the absolute abundance of the responses by the process of normalisation. An example of the results obtained in this way is shown in figure 5 in which 16 normal and 16 headache curves are superimposed.

It can be seen from this that all the curves follow the same general trend up to about 14 f/sec. then the broken lines separate from

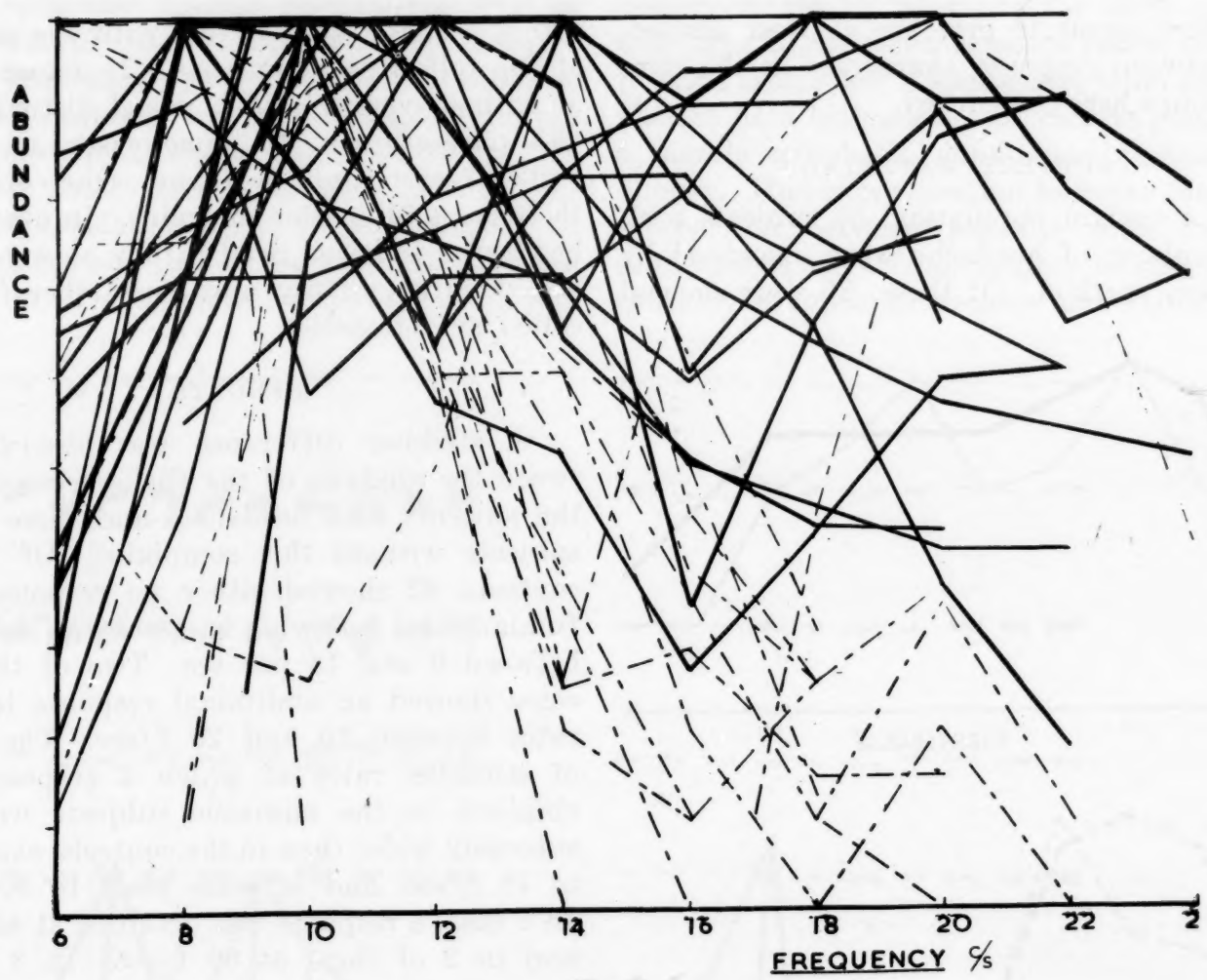


Fig. 5

Thirty-two frequency response curves superimposed. Sixteen of them, indicated by thick lines, are of subjects with migrainous headache and the sixteen curves represented by the broken line are from control subjects. Note the general separation of the dotted curves from the full ones from about 14 c/sec.

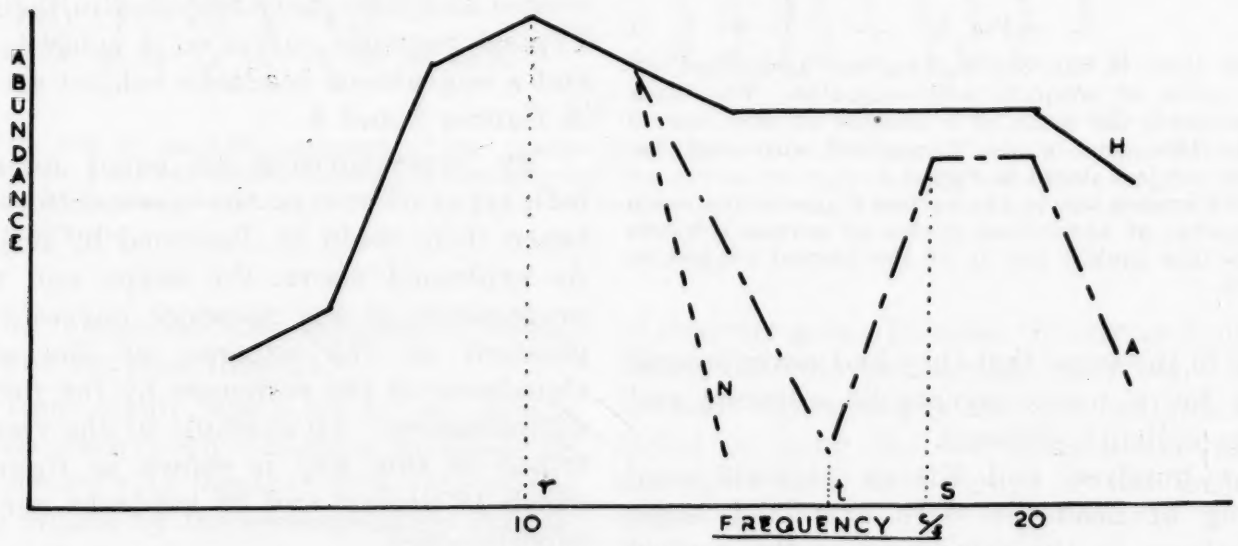


Fig. 6

Three distinct types of response curves as established in this investigation. The normal "N", migrainous "H" and a third type "A". The points at which measurements are made to form the criteria are at "r", "t" and "s".

the full ones. Two main classes of response curve emerge from this observation (*a*) that in which the response is maintained continously above 14 f/sec. (H, fig. 6) and (*b*) the response curve of the normals which falls away above about 14 f/sec. (N, fig. 6). Two of the curves shown in figure 5 behave a little differently from the others as they show a second distinct peak of response at a frequency higher than 14 f/sec., thus producing a trough in the curve at about 14-16 f/sec. (A, fig. 6). These two examples were in the control group and represent a small but quite definite class of response.

Having established the three types of response curve by graphic presentation it seemed desirable to devise a simple means of determining to which group a response belonged by direct inspection of the frequency analysis, thus eliminating the need for plotting graphs in every case.

Comparison of the ratio of the response abundance at different frequencies provides a suitable test. The points on the curve at which the abundance of the responses were to be compared were chosen empirically. It was found that three points, from which two ratios were formed, were sufficient to provide criteria for a good separation of the curves into their respective groups. The points were (*a*) at the frequency of the peak response in the alpha band (''r'' fig. 6); (*b*) at 18 f/sec. (''s'' fig. 6), and (*c*) at the trough, if any, between the other points (''t'' fig. 6).

The response at 18 f/sec. compared with that at the peak gave one ratio, the purpose of which was to separate groups A and H from group N (fig. 6). The second ratio, formed by the comparison of the response at the trough with the response at 18 f/sec., separated group H from group A. From consideration of superimposed curves in the form shown in figure 5 the following ratio values were found to give the best criteria of discrimination. The ratio value of

$$\frac{1}{3} \text{ for } \frac{\text{the response at 18 f/sec.}}{\text{the peak response}}$$

gave a good separation of type ''N'' from types ''A'' and ''H'' i.e. this ration $> \frac{1}{3}$ would signify an ''A'' or ''H'' type.

In the second ratio

$$\frac{\text{the response at the trough}}{\text{the response at 18 f/sec.}}$$

a value of $\frac{1}{2}$ gave the best result i.e. a value of $> \frac{1}{2}$ would indicate an ''H'' type.

It can be seen that to satisfy the criteria for an ''H'' type of frequency response, a curve must be continuous up to at least 18 f/sec. with little or no trough in the middle.

With this method of identifying the different types of frequency response, all the curves were re-examined using the above criteria to obtain a statistical analysis of the association of the type of response curve with the clinical picture (table I). For the purpose of this analysis the small ''A'' group which appeared in the control series was accepted as an ''N'' variation because there was no clinical evidence of specific abnormality in it. The responses of the 15 epileptic patients in the control group were similar to those of the normal subjects. The table shows that, by the chi-squared test of contingency, the association between the ''H'' type response curve and complaint of headache is extremely unlikely to be due to chance.

TABLE I

In the control group of normal and epileptic subjects, 16 per cent gave an ''H'' response

	''A'' or ''N'' Response	''H'' Response	Total
Normal	29	6	35
Epileptic	13	2	15
Total Controls	42	8	50

In the headache group, 96 per cent showed an ''H'' response

	''A'' or ''N'' Response	''H'' Response	Total
Headache Subjects	47	116	163
Grand total	5	108	113

$\chi^2 = 1{,}07$ $P > 10^{-6}$

Most of the patients in this series were examined several times, both before and after medical treatment. In many cases administration of the usual drugs such as carbachol and dihydro-ergotamine provided considerable relief, and a number of them were completely free from headaches for periods of over 6 months, but in none of these cases did the "H" type frequency response curve alter significantly. On several occasions it was possible to conduct the test during a headache attack, but again there was no significant change in the frequency response curve.

On the other hand, in two patients the "H" type curve was converted into a normal one for several hours after a procaine block of the cervical sympathetic system with the production of a Horner's syndrome. In these two cases temporary symptomatic relief was claimed by the patients.

One of these cases was submitted to cervical sympathectomy with resection of the superior cervical ganglion on the same side as that on which procaine injection had successfully abolished the effect. The operation was followed by a permanent Horner syndrome and there was relief from pain for some months, but the complaint returned and the "H" type response persisted throughout. In this case there was a history of cranial fracture.

In some three other fracture cases the migraine headache is localised to the fracture area. In one such old standing fracture case, migraine with or without epileptic discharge can be readily evoked by pressure due to a tight collar. All the post-traumatic cases with migraine evidenced undoubted psychological disturbance resembling that noted so frequently after cerebral commotion.

Since this survey was completed, a few patients complaining of paraesthesia of the face or upper extremities, together with a migrainous type of visual disturbance have been found to have a "H" type response curve although they denied ever having suffered from headache. Responses of the "H" type have also been found in two patients described as suffering from "abdominal migraine", with episodic attacks of severe abdominal pain followed by vomiting without apparent organic cause. Patients with pain referred to the trigemial nerve distribution do not show "H" type response curves.

DISCUSSION

A complaint of headache is one of the commonest causes of referral to a neurological clinic, but the relation of this complaint to other clinical features is sometimes obscure. All cases in this series complained of vomiting or visual disturbance or paraesthesia. This suggests involvement of some part of the nervous system as opposed to the intracranial structures presumed to be directly responsible for the pain referred to the head. The persistence of the "H" type frequency response curve even when the attacks were relieved by medication suggests that the peculiar response to flicker and headache have a common source; the dependence of both on the integrity of the cervical sympathetic chain seems to implicate this section of the autonomic system in both effects. This inference is reasonable on other grounds; in all the cases there was clinical evidence of autonomic disturbance during the attacks and in some there were signs of instability even between attacks. The inclusion in the group of patients with "H" type response curves, of several with a history of head injury may throw light on the mechanism involved; in these, as is common in post traumatic headaches, there was usually a marked exacerbation of the pain when the head was lowered, as in stooping. This effect suggest that the cardio-vascular homeostatic mechanism activated by changes in cranial blood pressure, presumably by way of the sino-aortic baro-receptors, are operating through an effector system which includes or affects the intracranial algesic structures. The relation of these mechanisms to cerebral activity as indicated by the flicker frequency response curves is still to be investigated. It should be recalled that Nakao, Ballin and Gellhorn (1956) obtained experimental evidence that, in cats, baro-receptor reflexes exert a homeostatic influence on the activity of the cerebral cortex; the peculiar effects of adrenaline and nor-adrenaline and of acetylcholine on in-

trinsic electro-cortical rhythms were reduced or abolished by sino-aortic denervation. This may well be related to the observation reported here on the results of cervical sympathetic blocking in two cases. On the other hand the persistence of the "H" type response curve during exhibition of the anti-sympatho-mimetic drug ergotamine suggests that the cerebral disturbance is not due directly to the action of adrenergic compounds, and it seems more likely that the intracranial barostatic processes are inculpated.

Experiments are now in progress to analyse in more detail the spatial distribution of the evoked potentials in these cases; with the aid of a two-channel analyser and toposcope it should be possible to decide whether the peculiar response to flicker at high frequencies is due to activation of the same brain structures as are responsible for the normal responses at lower frequencies, or to the recruitment of others. There is some evidence that, as in the animals studied by Nakao, Ballin and Gellhorn, the unusual activity at higher frequencies would suggest participation of the reticulo-thalamic structures rather than merely the specific projection pathways. Measurement of the critical frequency for flicker fusion might also be instructive.

The significance of postural change is also being studied with the use of a tilt-table and polygraphic recording of the relevant autonomic and somatic variables. Estimates of the catechol amine levels in blood and urine of these patients should also be of value in establishing the relationship between the electro-cerebral disturbance, the clinical complaint and the autonomic equilibrium.

SUMMARY

1. Frequency analyses of electroencephalograms from 50 subjects with no clinical complaint of headache and 113 suffering from episodic headache provide statistically significant evidence of a specific response spectrum to stimulation by flickering light in patients complaining of severe episodic headaches with associated nausea, vomiting and visual disturbances, or paraesthesia.

2. Two main types of fundamental frequency response curves were obtained:

(*a*) the "N" type in subjects without headache, with a peak in the alpha band and declining rapidly with increase of stimulus frequency above 14 f/sec.;

(*b*) the "H" type in patients complaining of headache, with a flat top showing a response maintained up to or above 20 f/sec.

3. A third type of frequency response curve was observed in a few patients in the control group; this showed a peak in the alpha band, a trough at about 14 f/sec. and a second peak at about 18 f/sec.

4. The three types of curve can be differentiated by direct comparison of the abundance of response at 18 f/sec. with that at the peak, and of the abundance at the trough to that at 18 f/sec.

5. Statistical analysis of the results showed that the odds against the association between the "H" type of frequency response curve and clinical complaint of headache being fortuitous are greater than a million to one.

6. The examination can be performed in approximately 2 min. with the aid of a frequency analyser and stroboscope and provides a useful method for the investigation of patients complaining of headaches, particularly those considered to be suffering from migraine.

7. No significant alteration in the flicker response curve has been observed during a headache attack and the conventional forms of medication have no apparent effect on the response, even when symptomatic relief is obtained.

8. Blocking the cervical sympathetic chain with procaine was followed by conversion of the "H" type to the normal curve for a few hours in the two cases tried, and both obtained symptomatic relief.

9. The spatial distribution of the cerebral mechanisms involved in the flicker response is being studied, together with the effect of postural change in order to test the hypothesis that the clinical and electro-cerebral features are both the result of disturbance in the cardio-vascular barostatic mechanisms.

RÉSUMÉ

1. Les analyses de fréquence des électro-encéphalogrammes de 50 sujets sans plainte subjective de céphalée, et de 113 sujets avec des céphalées épisodiques fournissent une évidence statistiquement significative d'un spectre de réponse spécifique à la stimulation lumineuse intermittente chez des malades souffrant de céphalée épisodique sévère, avec association de nausée, de vomissements, de troubles visuels, ou de paresthésies.

2. On a pu obtenir deux types principaux de courbes de réponse de fréquences fondamentales: *a*) le type "N" chez les sujets sans céphalée, avec un pic dans la bande alpha, et décroissant rapidement lors d'une augmentation de la fréquence du stimulus au-dessus de 14 f/sec.;

b) le type "H" chez les malades sujets aux céphalées, avec un sommet plat, démontrant une réponse maintenue jusqu'à, ou au-dessus de 20 f/sec.

3. Un troisième type de courbe de réponse de fréquence fut observé chez quelques malades du groupe de contrôle; dans celui-ci il y avait un pic dans la bande alpha, une activité de fond aux alentours de 14 f/sec., et un deuxième pic à 18 f/sec.

4. On peut différentier les trois types de courbes par la comparaison directe de l'abondance de réponses à 18 f/sec. avec celle au pic, et de l'abondance à du rythme de fond avec celle de la fréquence à 18 f/sec.

5. L'analyse statistique des résultats démontrait que les chances d'avoir une association fortuite entre le type H de la courbe de réponse de fréquence et la plainte clinique de céphalée sont plus grandes qu'un million pour un.

6. L'examen peut être fait dans un temps approximatif de deux minutes à l'aide d'un analyseur de fréquence et d'un stroboscope, et il fournit une méthode d'investigation utile chez les malades se plaignant de céphalées et en particulier chez ceux qui sont considérés comme des migraineux.

7. Il n'y a pas d'altération significative dans la courbe de réponse à la S.L.I. au cours d'une crise de céphalée, et les moyens habituels de médication n'ont aucun effet apparent sur la réponse, même quand un soulagement symptomatique est obtenu.

8. On a essayé, chez deux malades, le blocage à procaine de la chaîne cervicale sympathique, ce qui était suivi d'une conversion du type H à une courbe normale pendant quelques heures; les deux malades accusaient un soulagement symptomatique.

9. On étudie la distribution spatiale des mécanismes cérébraux qui sont impliqués dans la S.L.I., ainsi que les effets du changement postural, afin de mettre à l'épreuve l'hypothèse que les traits cliniques et électrographiques sont tous les deux le résultat de désordres des mécanismes cardio-vasculaires barostatiques.

ZUSAMMENFASSUNG

1. Frequenzanalysen des Elektroenzephalograms bei 50 Individuen, welche nicht an Kopfschmerzen litten, und bei 113 Individuen, welche episodischen Kopfschmerzen unterworfen waren, ergaben statistisch signifikante Indizien eines spezifischen Antwortspektrums auf intermittierende Lichtreizung, welches bei Patienten angetroffen wird, welche an episodischen, mit Nausea, Erbrechen, Sehstörungen oder Parästhesien einhergehenden Kopfschmerzen leiden.

2. Zwei Typen der fundamentalen Frequenzantwortkurve wurden gefunden:

(*a*) Der N- Typus bei Individuen ohne Kopfschmerzen mit einem Gipfel im Alpha-Band und raschem Abfallen in Bändern mit Reizfrequenz en über einem Wert von 14 Blitzen pro Sekunde.

(*b*) Der H-Typus bei Patienten, welche an Kopfschmerzen leiden und bei welchen ein flaches Plateau gefunden wird mit Reizantworten, welche aufrechterhalten werden bis zu einer Frequenz über 20 Blitzen pro Sekunde.

3. Ein dritter Typus der Frequenzantwortkurve wurde bei einigen wenigen Individuen der Kontrollgruppe beobachtet. In diesem Fall bestand ein Gipfel im Alpha-Band, ein Abfallen im Bereich von 14 Blitzen pro Sekunde, und ein erneuter Anstieg zu einem Gipfel im Bereich von 18 Blitzen pro Sekunde.

4. Die drei Kurventypen können differenziert werden durch einen direkten Ver-

gleich der Antwort im Band von 18 Blitzen pro Sekunde mit derjenigen am Gipfelwert, und mit den Werten am Tiefpunkt mit denjenigen im Band von 18 Blitzen pro Sekunde.

5. Eine statistische Auswertung der Befunde zeigte, dass die Wahrscheinlichkeit, wonach die Assozierung des H-Typus der Frequenzkurve mit Auftreten von Kopfschmerzen auf Zufall beruhen, könnte kleiner als 1 in 1 Million ist.

6. Die Untersuchung kann in ungefähr 2 Minuten ausgeführt werden mit Hilfe eines Frequenzanalysators und eines Stroboskops und kann als eine brauchbare Methode für die Untersuchung von Patienten mit Kopfschmerzen, speziell solchen mit Migräne, angesehen werden.

7. Während einem Kopfschmerzenanfall konnte keine signifikante Veränderungen der photischen Reizantwortskurve beobachtet werden, und die üblichen Formen der Medikation haben keinen augenscheinlichen Effekt auf das Reizantwortspektrum, selbst wenn symptomatische Beschwerdefreiheit erzeugt wird.

8. Blockierung des Halssympatikus mit Prokain erzeugte Veränderung des H-Typus zu einer Normalkurve welche für einige Stunden anhielt und symptomatische Beschwerdefreiheit wurde damit ebenfalls erzeugt.

9. Die räumliche Verteilung der zerebralen Mechanismen, welche in diesem Reizantworttypus mitspielen, und die Effekte von Lageveränderungen auf diese Reizantwort, bilden das Objekt einer weiteren Studie, welche zum Zweck hat, die Hypothese zu prüfen, wonach die mitgketeilten klinischen und elektroenzephalographischen Aspekte auf Grund von Störungen in barostatischen Kreislaufmechanismen erklärt werden können.

We are extremely grateful for the valuable guidance and stimulation suggestions given by Dr. Grey Walter and Dr. H. Crow.

We should also like to express our thanks to Miss V. Hallett for her assistance with EEG recordings, and to Mr. W. Warren for his technical co-operation.

RÉFÉRENCES

DOW, D. J. and WHITTY, C. W. M. Electroencephalographic changes in migraine; review of 51 cases. *Lancet*, **1947**, *2*: 52-54.

ENGEL, G. L., FERRIS, E. B. and ROMANO, J. Focal electroencephalographic changes during the scotomas of migraine. *Amer. J. Med. Sci.*, **1945**, *209*: 650-657.

MUNDY-CASTLE, A. C. The clinical significance of photic stimulation. *EEG Clin. Neurophysiol.*, **1953**, *5*: 187-202.

NAKAO, H., BALLIN, H. M. and GELLHORN, E. The role of the sino-aortic receptors in the action of adrenaline, nor-adrenaline and acetylcholine on the cerebral cortex. *EEG Clin. Neurophysiol.*, **1956**, *8*: 413-420.

SHAGASS, C. Clinical significance of the photomyoclonic response in psychiatric patients. *EEG Clin. Neurophysiol.*, **1954**, **6**: 435-445.

ULETT, G. A., CLESER, G., WINOKUR, G. and LAWLER, A. The EEG and reaction to photic stimulation as an index of anxiety proneness. *EEG Clin. Neurophysiol.*, **1953**, *5*: 23-32.

WALTER, W. GREY et SHIPTON, J. La présentation et l'identification des composantes des rythmes alpha. *EEG Clin. Neurophysiol.*, **1957**, Sup. No. 6.

WALTER, V. J. and WALTER, W. GREY. The central effects or rhythmic sensory stimulation. *EEG Clin. Neurophysiol.*, **1949**, *1*: 57-86.

Reference: GOLLA, F. L. and WINTER, A. L. Analysis of cerebral responses to flicker in patients complaining of episodic headache. *EEG Clin. Neurophysiol.*, **1959**, *11*: 539-549.

PRINTED IN CANADA

ELECTRONIC APPARATUS FOR BIOLOGICAL RESEARCH

by P. E. K. DONALDSON, M.A.

University of Cambridge

PRICE : $20.00 or 120s

This four-part handbook is addressed to those research workers and others in the biological field who are concerned in the possibilities, design, construction and maintenance of electronic equipment.

> "Donaldson, writing and working in a laboratory which has been a main centre of electrophysiology for fifty years and in the forefront of the biological use of electronic devices for more than thirty, has presented not only a compendium of the formal bones of these techniques, but also incorporated many of those little points of know-how that come from long practical experience. I think this book will be valuable both to the beginner entering this field and also to the more experienced, for its comprehensiveness makes it a reference work of electronics in biology."
>
> Professor Sir BRIAN MATTHEWS,
> *Physiological Laboratory, University of Cambridge*

Order from :

Canada: Butterworth & Co. (Canada) Ltd., 1367 Danforth Avenue, Toronto 6.

England: Butterworths Scientific Publications, 4 and 5 Bell Yard, London, W.C. 2.

U.S.A.: Academic Press Inc., 111 Fifth Avenue, New York 3, N.Y.

ANNOUNCEMENT

Supplement No. 14 of The EEG Journal is now available

THE BARBITURATE WITHDRAWAL SYNDROME

A clinical and electroencephalographic study

by

M. HERTEL WULFF,

Chief Psychiatrist, Sct. Hans Hospital, Roskilde, Denmark.

Order for immediate delivery from

or

Munksgaard,
Nörregade 6,
Copenhagen K., Denmark
(Price: Dan. kr. 28.-)

The EEG Journal,
3801, University Street
Montreal, Canada
(Price: $4.00)

EVIDENCE FOR THE EXISTENCE OF AN ELECTROENCEPHALOGRAPHIC SYNCHRONIZATION MECHANISM ORIGINATING IN THE LOWER BRAIN STEM [1]

J. Pierre Cordeau, M.D.[2] and Mauro Mancia, M.D.[3]

Istituto di Fisiologia della Università di Pisa e Centro di Neurofisiologia del Consiglio Nazionale delle Ricerche, Sezione di Pisa, Italia

(Received for publication: October 8, 1958)

INTRODUCTION

In recent experiments, Batini, Moruzzi, Palestini, Rossi and Zanchetti (1958, 1959) have shown that a midpontine pretrigeminal transection of the brain stem will alter the cat's electrocortical activity towards a nearly permanent state of desynchronization. To quote from their preliminary note (Batini *et al.* 1959): "While the normal intact cats, when isolated in a quiet environment, would display low voltage fast activity for not more than 20 to 50 per cent of the total recording time, a waking EEG persisted in the midpontine preparations for at least 70 and frequently 90 per cent of the total recording time in spite of the complete absence of any intentional stimulation." In an attempt to explain this temporal increase in EEG desynchronization patterns, they tentatively suggest the existence of a synchronizing or possibly sleep inducing influence in the caudal part of the brain stem. However, these authors also state: " . . . there is no evidence suggesting a parallel increase in the intensity of alertness".

In a recent series of experiments on cats (Cordeau and Mancia 1958), the asymmetry produced in the electrocortical activity of the two hemispheres by a mesencephalic hemisection alone was compared to that obtained when this hemisection is made in the midpontine pretrigeminal preparation. In the former case, as previously reported by Knott, Ingram and Chiles (1955) and by Rothballer (1956), the hemisphere ipsilateral to the lesion shows marked persistent synchronization. On the contralateral side the EEG varies in accordance with the behavioural state of the animal, being activated when the animal is awake and alert, synchronized when it is asleep. In the few days that follow the surgical procedure, the hemisphere overlying the mesencephalic hemisection can only be activated by rather strong auditory stimuli (police whistle) and this arousal is usually short lasting, sleep patterns reappearing soon after cessation of the stimulus. It was also reported that this asymmetry persists for a few days and fades gradually to reach full compensation in 6 to 8 days. At this stage the two hemispheres have similar and simultaneous EEG patterns. However, when the midbrain hemisection is made simultaneously with the complete midpontine pretrigeminal transection, the progression in time of the EEG patterns is quite different. While the animal shows periods of asymmetry with ipsilateral synchronization and contralateral activation as in the previous case, these alternate with prolonged periods of bilateral, low voltage high frequency activity where the asymmetry is absent. In other words, this cat's EEG behaves as if the animal were being submitted to strong and persistent alerting stimuli for long periods of time. Furthermore it was shown that the time necessary for compensation or disappearance of the asymmetry to occur, in the latter case, is

[1] This research has been sponsored jointly by the Office of Scientific Research of the Air Research and Development Command, United States Air Force, through its European Office, under Contract No. AF 61(514)-1125, and by the Rockefeller Foundation.

[2] Medical Research Fellow, National Research Council, Canada. Present address: Montreal Neurological Institute, Montreal, Canada.

[3] Fellow of the Consiglio Nazionale delle Ricerche, Roma, Italia.

usually shorter than when the midbrain hemisection is the only lesion. This was considered as further evidence that, as far as the electrocortical activity is concerned, the midpontine pretrigeminal preparation is on a high level of EEG activation, probably corresponding to that of the normal cat reacting to a strong alerting stimulus.

The present experiments were designed to test the hypothesis that the prolonged periods of low voltage fast activity and the high degree of EEG activation shown by the midpontine pretrigeminal cat is due to the withdrawal of some synchronizing or sleep inducing influence from the caudal parts of the brain stem as suggested by Batini, Moruzzi, Palestini, Rossi and Zanchetti (1958, 1959). To this end, midpontine pretrigeminal *hemi*sections were carried out, and the electroencephalograms of the chronic preparations recorded at regular intervals. The acute effects of hemilesions of the pons and medulla at various levels were also studied, in "encéphale isolé" preparations. The results obtained in both groups of experiments are considered valid arguments in favour of the above mentioned hypothesis.

METHOD

The method used has been described previously (Cordeau and Mancia 1958). In brief, under ether anesthesia the pontine hemisections were produced aseptically by electrolysis through a stereotaxically oriented electrode inclined at 30° from the vertical. Care was taken to produce minimal damage while entering and passing through the cerebellum and this organ was left in place. The reason for this departure from the procedure of Batini, Moruzzi, Palestini, Rossi and Zanchetti (1959), who removed the cerebellum after midpontine pretrigeminal transections was the following. The extreme extensor rigidity, elicited by the cerebellectomy, greatly increases the proprioceptive inflow to the reticular formation. The resulting EEG activation was likely to mask any asymmetry in the electrocortical activity of the two hemispheres in our preparations, in which the transection had been limited to one side of the brain stem.

Following surgery, the animals were given daily injections of penicillin and forced feeding used when necessary. Frequent recordings of the electrocortical activity were taken through permanently implanted brass screw electrodes, using an 8 channel inkwriter Galileo electroencephalograph.

In the case of acute experiments the observations were made on the "encéphale isolé" preparation with a section of the spinal cord at C_2 and artificial respiration. The same method as above was used for the midpontine and more caudal hemisections, while the midbrain lesions were also produced by electrolysis, but through a vertical electrode introduced anteriorly to the tentorium cerebelli.

At the end of the observation period the animals were killed, the brains fixed in 20 per cent formalin and the extent of the lesions controlled on Nissl and Weil stained sections.

RESULTS

1. *Chronic midpontine pretrigeminal hemisection.*

The lesions in this group of animals involved the whole *left* half of the pons, at a level just rostral to the site of entry of the trigeminal nerve. Following surgery, the animals were returned to their cages and left for a few hours to recuperate from the anesthesia. Recording usually started some 2 to 3 hours after the operation, and was repeated at frequent intervals and for long periods thereafter.

Typically, the animal with a midpontine hemisection showed highly activated, bilaterally symmetrical EEG patterns in the few hours that followed surgery. Whether this was due to the lesion itself or to the pain resulting from the operation is an open question. Some 6 to 12 hours post-operatively there usually began to appear in the electroencephalogram a few short episodes of synchronized activity. These rarely lasted longer than 40 to 60 sec. at first, and were either confined to the *right hemisphere* (*contralateral* to the side of the lesion) (fig. 1 A and fig. 2) or else began there and only became bilateral after the first few spindles had appeared on the right side (fig. 1 B and C). The individual spindles of the right hemis-

phere at the beginning of each episode were usually of rather low voltage and short duration, as if cut short before reaching their full development. At times, they would attain their full size and well known fusiform shape only after spreading to the left hemisphere. But this was not a constant finding and some synchronized episodes, while entirely limited to the right hemisphere, would show the usual complete and well formed spindle bursts. During these periods, when synchronization had become bilateral, it was often seen, by recording at high paper speeds, that individual spindles would begin on the right hemisphere first and spread to the left only after the first two to three waves.

These episodes of synchronization were usually short lasting, and were separated by long periods where the electrocortical activity remained highly desynchronized corresponding to the EEG of the very alert animal. However, recording at high paper speeds and with a longer time constant during these activation periods often showed slower component frequencies in the electrocortical activity of the right hemisphere.

This alteration of short episodes of asymmetrical synchronized activity with longer periods of bilateral activation usually persisted practically unchanged for the next few days. At times, considerable patience on the part of the observer was necessary to record

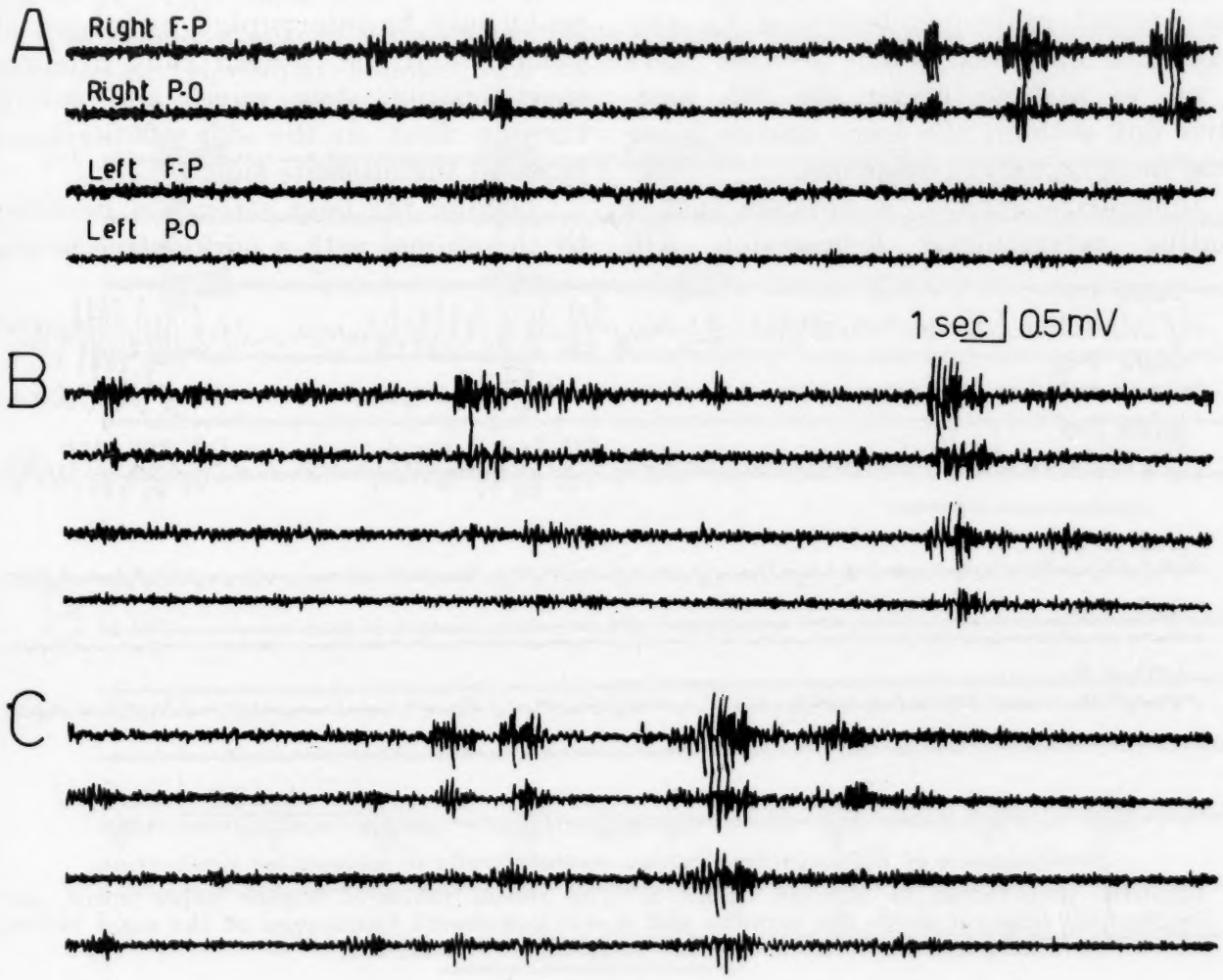


Fig. 1

Predominance of EEG synchronization contralaterally to midpontine hemisections.

The chronic midpontine hemisection at a level just rostral to the point of entry of the trigeminal nerve was performed on the *left* side. The record was taken on the day after the operation. A, B and C are continuous and show one of the synchronization episodes described in the text. Note the spindles which appear over the *right* hemisphere first and only become bilateral after 40 sec.; moreover they remain of higher amplitude and longer duration on the right hemisphere. This episode is short lasting as usual, and bilateral desynchronization supervenes at the end of the lower tracing.

a few of these synchronization episodes. It was only occasionally that bilateral sleep patterns could be recorded for any length of time. Even at this time, however, the record sometimes showed more frequent, higher amplitude and longer lasting spindles over the right hemisphere, i.e. on the side opposite to that of the section. Each of these episodes of synchronization could easily be interrupted and an arousal pattern substituted by any mild alerting stimulus. Such records were taken up to and including the 5th post-operative day without any basic change being observed in the patterns described.

To summarize briefly, it appears that a midpontine petrigeminal hemisection will produce an asymmetry in the electrocortical activity of the two hemispheres. This asymmetry is characterized by the greater tendency to synchronization shown by the *contralateral* hemisphere, or expressed differently and perhaps more accurately by the greater tendency of the ipsilateral cortex to remain permanently activated. Moreover, the general level of alertness of the animal, at least as far as its electrocortical activity is concerned, is raised and lengthened in a manner somewhat similar to the midpontine pretrigeminal preparation (Batini, Moruzzi, Palestini, Rossi and Zanchetti 1958, 1959).

This whole EEG behaviour stands in sharp contrast to the asymmetry obtained following a chronic hemisection at mesencephalic level (Knott, Ingram and Chiles 1955; Cordeau and Mancia 1958). It will be remembered that with such a lesion, the cat showed consistently a greater tendency to synchronization over the ipsilateral hemisphere, where the sleep patterns persisted practically unchanged throughout the 3 to 4 days that followed surgery. This ipsilateral synchronization could only be interrupted by strong alerting stimuli, and the arousal thus produced was short lasting, slow waves and spindles returning first on the side of the lesion and later on the opposite side.

During the long activation periods shown by the animal with a midpontine hemisection, the effects of small doses of Nembutal injected intravenously were studied. At times, a very small dose of this drug (0.5 to 1 mg/kg.) would bring out an EEG asymmetry stronger than that occurring during spontaneous synchronization, with well developed spindles appearing in an isolated fashion in the EEG of the hemisphere *contralateral* to the lesion. These small doses did not affect the animal's responsiveness to arousal stimuli, which constantly disrupted the synchronous rhythms. At other times, and usually with larger doses, the resulting synchronization was bilateral, but began on the right side where it often remained more marked.

From the behavioural standpoint these

Fig. 2

Predominance of EEG synchronization contralaterally to midpontine hemisection.

Identical preparation to that of figure 1. The record taken at higher paper speed and longer time constant shows the spindles and slower component frequencies of the right cortex, i.e. of the hemisphere *contralateral* to the midpontine hemisection.

animals did not show the degree of excitation which could have been expected from the predominantly activated EEG pattern. They would lie quietly but alert in their cages unless disturbed and, following stimulation or prodding, soon relapsed into their former state of motionless alertness.

2. *Acute midpontine pretrigeminal hemisection in an "encéphale isolé" cat.*

In this second group of animals the same midpontine pretrigeminal hemisections were repeated under ether anesthesia. The spinal cord was then transected at C_2, anesthesia discontinued and artificial respiration begun. The cats were then taken out of the Horsley-Clarke apparatus and left to recuperate in a dark quiet room.

One to two hours after the end of the operation, there began to appear in the bilaterally activated EEG, short periods of synchronized activity which were confined to the right hemisphere (*contralateral* to the pontine hemisection), while the left remained desynchronized. At times, these short burst gradually lengthened and became more frequent, until a stage was reached at which the right hemisphere showed nearly continuous synchronization (fig. 3 A). These sleep patterns occasionally spread to the left hemisphere, but they were usually short lasting on this side. During these periods of one sided synchronization, slight involuntary alerting stimuli, such as a fortuitous noise in the room or a change in the lighting, or intentional stimulation (soft whistle or touch of the whiskers), were usually sufficient to produce a prolonged arousal (fig. 3 A). But when the synchronization returned, it was again pre-

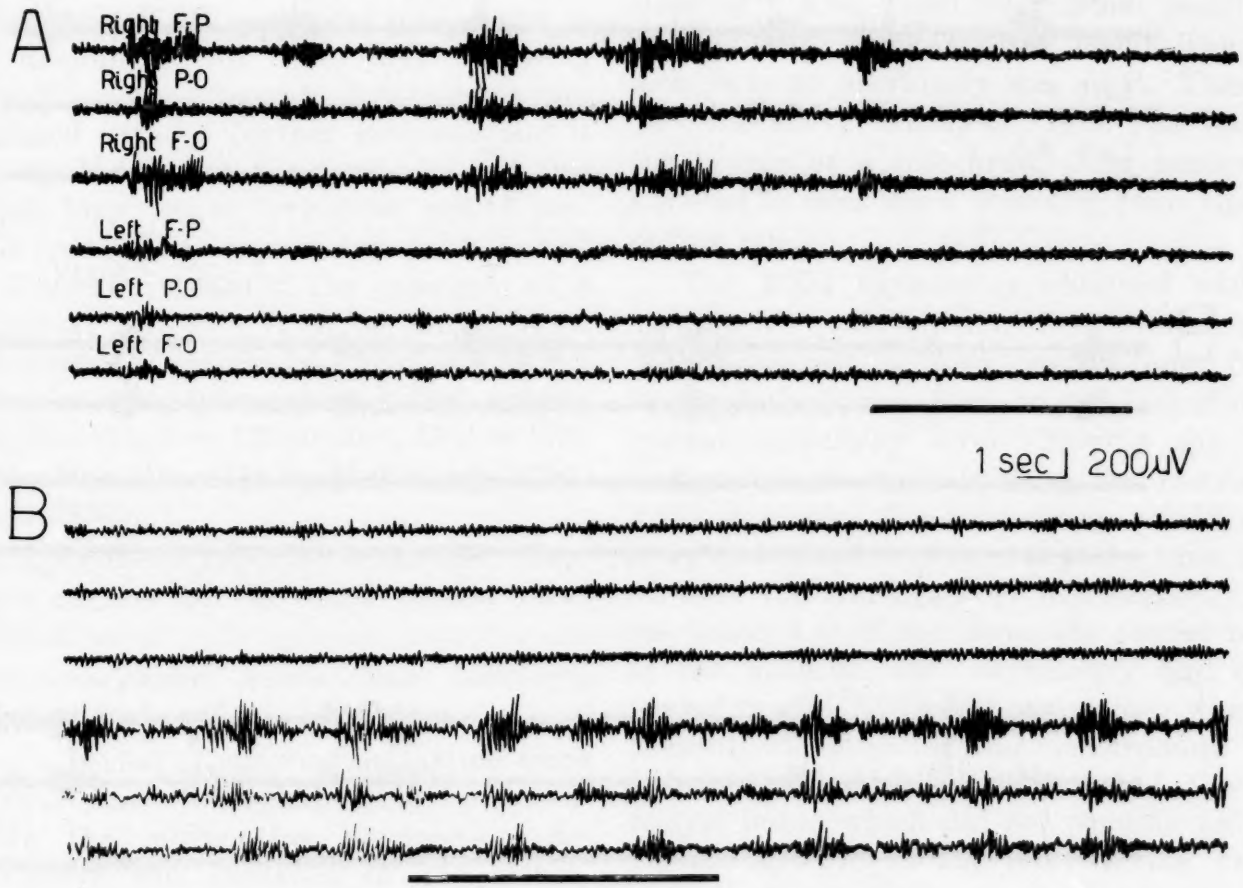


Fig. 3

Shift from contralateral to ipsilateral EEG synchronization following a second hemisection at midbrain level.

A. *Left* midpontine hemisection in an "encéphale isolé" preparation. During a period of spontaneous EEG synchronization the spindles are present in the *contralateral* hemisphere only and a mild auditory stimulus (soft whistling) produces a desynchronization. B. Same cat after new hemisection at the level of the midbrain and on the same side as the pontine lesion. Note shift in the EEG asymmetry. The *ipsilateral* hemisphere is now deeply synchronized and a strong alerting stimulus (police whistle) is ineffective in producing an arousal. The dark line underneath each record shows the time of stimulation.

dominant or confined to the hemisphere on the side opposite to the lesion.

More frequently, however, the ''encéphale isolé'' preparation with the midpontine hemisection showed nearly permanently desynchronized activity with very little tendency to drowsiness or sleep. At this time, the i.v. injection of small doses of Nembutal (0.5 to 1 mg/kg.) facilitated the appearance of the stant finding, consists in the increased tendency to drowsiness and sleep of the ''encéphale isolé'' cat.

The EEG asymmetry resulting from chronic or acute midpontine pretrigeminal hemisections, speaks in favour of the hypothesis of Batini, Moruzzi, Palestini, Rossi and Zanchetti (1958, 1959) that a tonic synchronizing influence arises from the caudal part

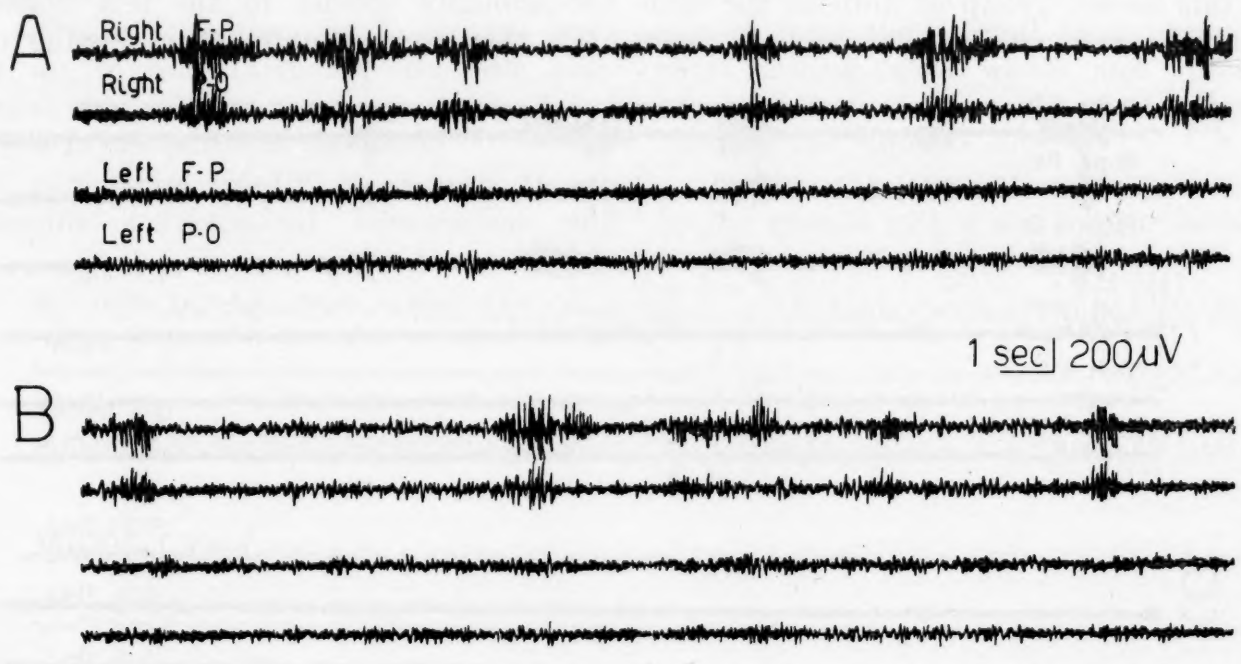


Fig. 4

EEG asymmetry produced by a small dose of Nembutal following acute midpontine hemisection. Left midpontine hemisection in an ''encéphale isolé'' preparation. The electrocortical activity of this animal remained desynchronized for 2½ hours following the end of the surgery. A, B and C are continuous and show the synchronization of the *contralateral* hemisphere 2 min. after the i.v. injection of 0.5 mg/kg. of Nembutal.

EEG synchronization in the hemisphere *contralateral* to the section (fig. 4). With these small doses, the animal retained its responsiveness to arousal stimuli.

To sum up, the acute midpontine hemisection in the ''encéphale isolé'' preparation will reproduce the same electrocortical asymmetry as this chronic section alone. The only possible difference, and this was not a constant finding, consists in the increased tendency to drowsiness and sleep of the ''encéphale isolé'' cat.

The EEG asymmetry resulting from chronic or acute midpontine pretrigeminal hemisections, speaks in favour of the hypothesis of Batini, Moruzzi, Palestini, Rossi and Zanchetti (1958, 1959) that a tonic synchronizing influence arises from the caudal part of the brain stem. In order to explain our results the assumption should be made that this influence facilitates the EEG synchronization of the hemisphere *contralateral* to the lesion through the intact half of the brain stem. It is prevented from doing so by the pontine hemisection on the injured side, where the cortex remains predominantly desynchronized.

However, two other possibilities should be eliminated before the lower brain stem origin of this synchronizing influence can be accepted. First, convincing evidence should be provided that we are not dealing with some kind of "irritation" of critical neuronal structures belonging to the ascending reticular system (Moruzzi and Magoun 1949); an asymmetrical irritation which would be directly or indirectly related to the electrolytic lesion. It is true that such an irritation appears unlikely since the EEG syndrome was shown to persist unchanged for five days following the operation. Its existence, however, cannot be dismissed without further evidence and it must be conceded that the persistence of this unilateral, long lasting irritation, would produce the same EEG asymmetry as described above. Secondly, granted the existence of a synchronizing influence from the caudal brain stem, it might be maintained that this effect is due to the tonic baroceptive inflow arising in the pressoreceptors (Bonvallet, Dell et Hiebel 1954; Mazzella, García Mullin and García Austt 1957).

The experiments reported in the next chapters were carried out in order to test these possibilities.

3. *Mesencephalic hemisection following hemipontine transection.*

After a period of observation lasting some 3 to 4 hours, the "encéphale isolé" preparation with the midpontine hemisection described above was replaced in the stereotaxic apparatus. Using the same technique, a second hemisection was then carried out a few mm. anteriorly, i.e. at the intercollicular level and on the same side as the pontine section. Following this second intervention and with the cat in the same conditions as previously, a dramatic shift in the EEG asymmetry occurred (fig. 3 B). On the side of both the mesencephalic and pontine lesions, the cerebral hemisphere was now deeply and permanently synchronized, and this synchronization had a tendency to spread to the right hemisphere. Arousal stimuli, while producing a right sided arousal easily, were not always effective in activating the left hemisphere (fig. 3 B). This new asymmetry between the two cortices persisted unchanged to the end of the observation period some 2 to 3 hours later. It has been shown previously (Cordeau and Mancia 1958) that the EEG asymmetry produced by a mesencephalic hemisection will persist from 5 to 8 days before compensation occurs.

4. *Hemisections caudal to the midpontine level.*

In this series of acute experiments, the brain stem hemisection was moved caudally in steps of 2 mm., from its original position at the midpoint pretrigeminal level. The same technique as previously was used. Therefore each successive "encéphale isolé" cat was now the bearer of a left brain stem hemisection situated 2 mm. more caudally than the preceding one.

The EEG asymmetry obtained with the midpontine pretrigeminal hemisection, recurred unchanged in these preparations, for all levels of the lesion down to and including the rostral medullary level. Moving the hemisection 2 mm. caudally from the rostral medulla decreased the asymmetry considerably, sleep patterns being only slightly more marked over the contralateral hemisection. With the lesion 4 to 6 mm. from the rostral border of the medulla, this asymmetry had disappeared and EEG synchronization, whenever present, was bilateral and synchronous. Anatomical controls have shown that the most rostral lesion which did not produce an EEG asymmetry was at the level of the *nucleus paraolivaris medialis.*

5. *Midpontine pretrigeminal hemisection in the "encéphale isolé" cat with denervated carotid sinuses and bilateral vagotomy.*

The same sequence of events described under 2 was followed here. This involved the placing of the pontine lesion, section of the cord at C_2 and recording of the EEG following disappearance of the ether anesthesia. With the electrocortical asymmetry present in the record, both carotid sinuses were then denervated and a bilateral vagotomy performed. Subsequent records showed that the original asymmetry persisted unchanged following the denervation of the carotid sinuses and section of both vagi (fig. 5). In other words, the hemisphere contralateral to the

midpontine hemisection still showed the greater tendency to synchronization.

In a few cases a slightly different procedure was used. After the midpontine hemisection and before transection of the spinal cord at C_2, the cat was curarized, the blood pressure from the femoral artery was recorded and its changes during occlusion of both carotids used as an index of the effectiveness of our denervation technique. Both, the abrupt rise in blood pressure immediately following section of the Hering nerve and the subsequent absence of the effects of carotid occlusion substantiated our claim to a complete denervation. Both vagi were then sectioned, the spinal cord interrupted at C_2, and the EEG recorded. This showed the same asymmetry as in the other groups of experiments.

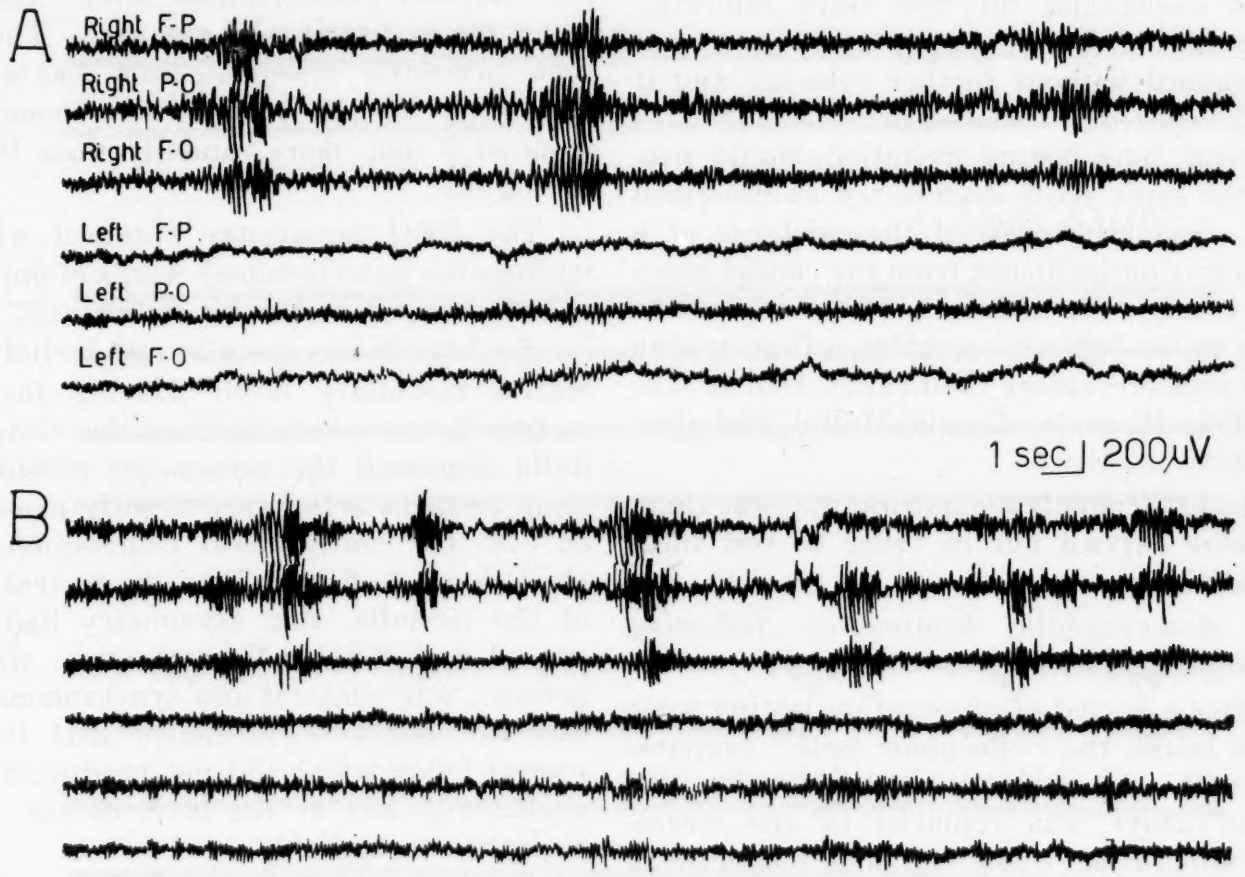


Fig. 5

Persistent EEG asymmetry following bilateral carotid sinus denervation and vagotomy.

A. *Left* midpontine hemisection in an "encéphale isolé" preparation. During a period of synchronization the spindles are present in the *contralateral* hemisphere only. B. Same cat after bilateral denervation of the carotid sinuses and vagotomy. The EEG asymmetry is unchanged.

DISCUSSION

In an attempt to explain the temporal increase in EEG activation patterns recorded in the chronic midpontine pretrigeminal cat, Batini, Moruzzi, Palestini, Rossi and Zanchetti (1958) wrote that "a synchronizing or possibly sleep inducing influence in the caudal brain stem could be tentatively envisaged..." In a recent publication (Cordeau and Mancia 1958), we have shown that the midpontine pretrigeminal cat, as far as its electrocortical activity is concerned, is on a high intensity level of EEG activation, a level which probably corresponds to that of the normal cat reacting to a strong alerting stimulation. In that paper also the hypothesis of a release from a synchronizing influence arising from the caudal brain stem was considered to explain this intensity of EEG alertness. The present series of experiments provides strong, if somewhat indirect evidence, in favour of this hypothesis. The pontine hemisections, either chronic or acute, produce an asymmetry in the electrocortical activity of the two hemispheres. The ipsilateral cortex shows strong and persistent activation patterns,

somewhat similar to those of the pretrigeminal preparation, while the contralateral hemisphere, still connected to the caudal brain stem, is the one predominantly and primarily affected when EEG synchronization occurs.

The first task of our discussion is to see whether the alternative explanation of a long lasting, unilateral "irritation" might also account for our findings. The term "irritation" is used in the wide sense of the word, indicating any increase in the activity of the neurons lying immediately above the lesion which is not due to a release from a tonic inhibitory control. There is little doubt that if such an increase of activity were to remain localized to the units of the ascending reticular system lying immediately above the unilateral midpontine lesion, and persist unabated for several days, this "irritative" change could also account for our findings.

We believe that this possibility is made very unlikely, though not completely eliminated, by several considerations.

First, the EEG asymmetry obtained from a chronic midpontine hemisection persisted unchanged for five days, the longest period of observation. It is difficult to believe that an "irritative" focus would remain localized for such a long period of time, when it is well known that electrical stimulation of the same pontine structures, will produce *bilateral* EEG arousal. Any recent irritative event, either gradually fades away or has a tendency to grow in both its temporal and spatial aspects. Secondly, following a more rostral hemisection at the intercollicular level in the same animal, a dramatic shift in the asymmetry occurred with ipsilateral synchronization replacing the predominantly activated EEG patterns. It is not easy to explain why irritation of structures immediately overlying the lesion should produce opposite effects depending on the site of the electrolytic destruction at pontine or midbrain levels, in view of the fact that electrical stimulation of both regions of the brain stem will produce the same patterns of EEG arousal. Finally, hemisections performed in successive animals and at lower brain stem levels down to and including the rostral medulla were followed by the same EEG asymmetry as the midpontine hemisection. This effect was markedly decreased, however, with the hemisection at a slightly more caudal level and it disappeared when the lesion was placed caudally to the midmedullary level. In the latter case, when sleep patterns appeared in the electrocortical activity, they did so in a bilaterally synchronous manner. It is unlikely that the brain stem hemisection could produce an irritation in pontine structures sufficient for prolonged and intense ipsilateral activation to persist in the EEG for a few days while being unable to do so even for a few hours at mesencephalic and medullary levels.

To state that the midpontine transection interrupts an ascending flow of synchronizing impulses, does not imply necessarily that this influence arises within the lower brain stem. It could be mediated by structures, not necessarily reticular in character, lying in this area of the central nervous system. Bonvallet, Dell, and Hiebel (1954) were the first to show that sino-aortic denervation resulted in EEG activation, an effect which might of course be explained simply with a marked increase in adrenaline discharge. Although there is no evidence that the tonic inflow of baroceptive impulses, which is present for normal levels of blood pressure, exert a synchronizing influence on the EEG through ascending pathways, Bonvallet, Dell and Hiebel (1954) and Mazzella, García Mullin and García Austt (1957) stated that the experimental distension of the carotid sinuses produced EEG synchronization. The possibility that this peripheral synchronizing influence may have been responsible for the EEG asymmetry recorded in the present experiments was eliminated since the greater tendency to synchronization in the hemisphere contralateral to the midpontine hemisection persisted unchanged after denervation of both carotid sinuses and bilateral vagotomy. These findings obviously do not eliminate the possibility that a tonic baroceptive barrage may at times contribute to the production of EEG sleep patterns. But they do show that this afferent inflow is not an essential element in the production of the asymmetry observed here.

Summing up, it seems that the present

results can best be explained by assuming that an ascending flow of impulses originating in the lower part of the brain stem and endowed with a synchronizing influence on the electrocortical activity, can affect the hemisphere overlying the intact half of the brain stem, but are prevented from doing so on the side of midpontine lesion. This flow may be influenced, but is not conditioned by the tonic barrage of baroceptive impulses. The EEG arousal obtained by Magni, Moruzzi, Rossi and Zanchetti (1959) with the injection of barbiturates in the lower brain stem circulation, could also be explained by the same hypothesis.

The general characteristics of this synchronizing or sleep including mechanism, such as its anatomical boundaries, possible afferent components, mechanism of action and rostrally oriented efferent pathways, are largely unknown. However it may be useful to review briefly what can be learned of its properties from the present study or surmised from current literature.

Anatomically, this synchronizing influence would arise from structures situated between the rostral level of the medulla and the first cervical segments of the spinal cord. It is present in the "encéphale isolé" preparation and its manifestations are clear for brain stem hemisections down to and including the rostral medullary level. However, these limits cannot be fixed accurately by the method used here.

Little can be said concerning the possible tonic activity of these synchronizing structures or the afferent impulses which may contribute to this tonicity. One likely candidate for the latter, though not an essential one, would be the synchronizing influence of the afferent inflow from carotid and cardioaortic pressoreceptors (Bonvallet, Dell and Hiebel 1954; Mazzella, García Mullin and García Austt 1957).

The mechanism of action of this synchronizing influence is also a matter for conjecture. As a first approach three possibilities could be considered: (1) EEG synchronization through direct action on cortical neurons; (2) inhibition of the ascending brain stem activating system; (3) "facilitation" of, or synergetic action with the so-called thalamic pacemaker which seems to be involved in some way in the production of cortical sleep spindles.

Nothing can be said concerning the first two possibilities and further experimentation is needed before these can be discussed. However, there exists some experimental support for the third hypothesis. In a recent report (Cordeau and Mancia 1958) we compared the electrocortical activity of cats with mesencephalic hemisections to that of the midpontine pretrigeminal preparation with the same lesion. It will be remembered that the midbrain hemisection alone results in a strong *ipsilateral* synchronization of the EEG. This synchronization lasts a few days, fades gradually, and the asymmetry in the cortical activity of the two hemispheres has usually disappeared by the 6th to 8th post-operative day. Following this compensation, when the animal becomes drowsy or goes to sleep spontaneously, or else after the injection of a small dose of Nembutal (0.5 to 1 mg/kg.), sleep spindles often appear first on the hemisphere *contralateral* to the midbrain hemisection. The animal with both a mesencephalic hemisection and a midpontine transection shows a somewhat similar initial asymmetry and compensation with time (the reader is referred to the original paper for details). However, following compensation this paradoxical appearance of spindles on the contralateral hemisphere is never seen. Following the injection of small doses of Nembutal (0.5 to 1 mg/kg.), the spindles always appear on the hemisphere *ipsilateral* to the midbrain lesion before becoming bilateral. When we reported these apparently contradictory findings no explanation was attempted. However, with the present hypothesis of a synchronizing influence originating in the lower brain stem, this explanation becomes possible. As far as the brain stem activating system is concerned, both preparations are in somewhat identical conditions. Each is left with an efficient activating system on one side of the brain stem only, that is, on the side opposite to the midbrain hemisection. If "going to sleep", either spontaneously or following the injection of Nembutal, were only the result of a decrease

in activity of the brain stem activating system, spindles should appear first in the hemisphere overlying the midbrain hemisection, as they do in the pretrigeminal preparation, since on that side the tonic barrage of activating impulses is greatly decreased. However, if we assume that "going to sleep" also involves the participation of a synchronizing mechanism originating in the lower brain stem and acting on the thalamic spindle pacemaker, the integrity of this link in one half of the brain stem of the compensated hemimesencephalic cat might explain the appearance of spindles on that side first, when the animal goes to sleep spontaneously or following the injection of a small dose of Nembutal. With the additional, complete midpontine transection, this link is interrupted bilaterally and spindles always appear in the hemisphere overlying the midbrain lesion first.

This hypothesis of a facilitatory action of the bulbar synchronizing centre on the thalamic spindle pacemaker might also explain bursts of unit activity recorded with microelectrodes from the midbrain reticular formation. According to Machne, Calma and Magoun (1955) these bursts of unit activity are synchronous with cortical spindles and disappear during the interspindle lulls or following cortical arousal. To date, the firing of these units has been interpreted as the result of the cortical spindles rather than its cause (Moruzzi 1956; see also Rossi and Zanchetti 1957). But the reverse may be true. These bursts of unit activity in the midbrain reticular formation could be rostrally oriented impulses from the bulbar synchronizing centre to the thalamic pacemaker, travelling over multisynaptic neuron chains.

Sporadically in current neurophysiological literature, the observation is made, either incidental to the experiments described or as a definite aim of the research, that electrical stimulation of the midbrain reticular formation under various conditions, will produce a "flattening" of the electrocortical activity (Moruzzi and Magoun 1949; Domino 1955; Ingvar and Söderberg 1958) or a definite synchronization with true sleep patterns in the EEG (Caspers und Winkel 1954; Caspers 1955, Proctor, Knighton and Churchill 1957; Ingvar and Söderberg 1958; see also Rossi and Zanchetti 1957).

Domino (1955) has suggested that the "flattening reaction" which he obtained following stimulation of the midbrain reticular formation after the injection of pentobarbital or of large doses of Mephenesin, should be considered as evidence for the existence of an ascending "deactivating" mechanism. In the examples shown and according to his description, the stimulation of the reticular formation produces a reduction of the spindling frequency or a complete flattening of the EEG. We believe that a distinction should be made between such a "deactivating" mechanism as postulated by Domino and a truly synchronizing system whose function would be to facilitate the appearance of spindles and slow waves in the electrocortical activity. In the former case, the mechanism involved in the "flattening reaction" would appear to be an inhibition or a desynchronization of the thalamic pacemaker interested in the production of the cortical spindling activity, while in the latter the reverse would be true. In other words it is our opinion that the "flattening reaction" is more likely to be the result of the stimulation of an activating mechanism rather than that of a synchronizing one.

For this reason we prefer to limit our discussion to those cases where behavioural sleep or true EEG sleep patterns were produced by electrical stimulation of the brain stem, usually with low voltage, low frequency electrical pulses (Caspers und Winkel 1954; Caspers 1955; Proctor, Knighton and Churchill 1957; Ingvar and Söderberg 1958). In these cases it may be that the stimulation has selectively or primarily influenced the rostrally oriented pathways from the bulbar synchronizing structures rather than the surrounding activating neurons of the midbrain.

The rarity with which these effects are reported suggests that the neurons or fibers belonging to the synchronizing pathways must be dispersed diffusely in the midst of the more potent activating ones or else segregated in an area seldom explored by the stimulating electrode. The former possibility is the more probable one since increasing the intensity or frequency of the stimulation usually reverses

the effect to one of activation. The experimental situations which condition this selective activation of synchronizing fibers are not apparent from a perusal of the literature. The same explanation may be valid for the thalamic ''sleep inducing centre'' of Hess whose low frequency stimulation produces both behavioural (Hess 1949) and EEG sleep (Hess jr., Koella and Akert 1953) patterns in the electrocortical activity. This diencephalic locus could be the concentrated thalamic end of the postulated synchronizing pathway. It is quite evident that more experimentation is needed before these questions are solved satisfactorily.

As a final remark, the existence of a synchronizing mechanism originating in the caudal part of the brain stem, raises the question of its functional relationship with the inhibitory centre of Magoun and Rhines (1946). Following a recent series of experiments, Hugelin and Bonvallet (1957a, 1957b, 1957c) suggest that the cortical activating influence of the brain stem reticular formation and its facilitatory action on postural tonus and phasic movements are two aspects of the same single system. They are led to this conclusion from the close parallelism which exists in the ascending and descending manifestations of this system, it being impossible to dissociate the two or to influence one without simultaneously producing a similar change in the other. At this stage, nothing justifies a similar assumption for the brain stem synchronizing mechanism and the inhibitory centre of Magoun and Rhines. However, in view of the roughly similar anatomical boundaries of the two systems and the fact that the same peripheral stimulus, i.e. a distension of the carotid sinus, will synchronize the electrocortical activity (Bonvallet, Dell et Hiebel 1954; Mazzella, García Mullin and García Austt 1957) and will also inhibit the ventral root monosynaptic reflex possibly through a direct action on the inhibitory centre (Dell, Bonvallet et Hugelin 1954), the hypothesis of a close functional relationship, if not complete identity, between the two should be considered and made the subject of further study.

SUMMARY

The aim of the present investigation was to test the hypothesis made by Batini, Moruzzi, Palestini, Rossi and Zanchetti (1958, 1959) of an EEG synchronizing influence originating in the caudal part of the brain stem. To this purpose, the electrocortical activity of cats with chronic midpontine pretrigeminal hemisections was recorded. It was found that such a lesion produced an asymmetry in the EEG of the two hemispheres, the *contralateral* side showing the greater tendency to synchronization, while the ipsilateral hemisphere remained persistently desynchronized. The same EEG asymmetry was found to exist when the acute effects of brain stem hemisections were studied in the ''encéphale isolé'' preparation and for all levels of the lesion from the pretrigeminal down to the rostral medulla. The EEG asymmetry was not present with hemisections caudal to the mid- medullary level. Control experiments have shown that this asymmetry is unlikely to be due to an irritation of the ascending reticular system by the lesion and resulting ipsilateral desynchronization. In similar experiments the EEG asymmetry was found to persist after denervation of both carotid sinuses and bilateral vagotomy. Therefore the synchronizing effect of pressoceptive afferent impulses is not essential to the asymmetry observed.

These results are considered as valid evidence in favour of the existence of a ''synchronizing mechanism'', originating in the caudal part of the brain stem. This mechanism influences the hemisphere contralateral to the pontine hemisection, where sleep patterns were seen, through the intact half of the brain stem, while it is prevented from doing so on the side of the lesion, where the electrocortical activity remained predominantly desynchronized.

The possible characteristics and properties of this synchronizing mechanism are discussed in the light of present day knowledge concerning the control of the electrocortical activity in the cat.

RÉSUMÉ

Le but de ce travail a été de contrôler la validité de l'hypothèse émise par Batini, Moruzzi, Palestini, Rossi et Zanchetti (1958, 1959) concernant l'existence d'une influence synchronisante sur l'activité électrocorticale, dont l'origine se trouverait dans la partie cau-

dale du tronc cérébral. A cette fin nous avons enregistré l'activité électrocorticale du chat porteur d'une hémisection chronique du tronc cérébral, placée juste en amont de la zone d'entrée du trijumeau dans le tiers moyen de la protubérance (hémisection prétrigéminale). A la suite de cette lésion, nous avons noté une asymétrie de l'activité EEG des deux hémisphères cérébraux, l'hémisphère contralatéral à l'hémisection présentant une plus forte tendance à la synchronisation tandis que l'ipsilatéral reste désynchronisé d'une façon quasi permanente. Nous avons retrouvé la même asymétrie chez le chat ''encéphale isolé'' porteur d'une hémisection du tronc cérébral située, soit au niveau prétrigéminal, soit plus caudalement, jusqu'à la partie rostrale du bulbe. L'asymétrie électroencéphalographique n'est plus présente si l'hémisection du tronc cérébral est placée caudalement à la partie moyenne du bulbe. Des expériences de contrôle nous permettent d'affirmer: 1) que les afférences baroréceptives du sinus carotidien ou de la zone aortique ne sont pas essentielles pour que se manifeste cette asymétrie, et 2) qu'il est peu probable que cette asymétrie soit attribuable à une irritation locale du système activateur réticulaire par la lésion elle-même.

Par conséquent ces résultats sont considérés des arguments valides en faveur de l'hypothèse d'un ''mécanisme synchronisateur'' qui trouverait son origine dans la partie caudale du tronc cérébral. Ce mécanisme synchronisateur manifeste son influence sur l'hémisphère cérébral contralatéral à l'hémisection, par l'intermédiaire de la zone intacte du tronc cérébral. C'est en effet dans l'activité EEG de cet hémisphère que nous avons noté la présence d'ondes lentes et de ''spindles''. L'hémisection empêche cette influence d'atteindre l'hémisphère ipsilatérale où l'activité EEG reste à prédominance désynchronisée.

ZUSAMMENFASSUNG

Das Ziel der vorliegenden Untersuchung bestand darin, die von Batini, Moruzzi, Palestini, Rossi und Zanchetti (1958, 1959) aufgestellte Hypothese zu prüfen, wonach der kaudale Abschnitt des Hirnstamms einen synchronisierenden Einfluss auf das EEG ausübt. Zu diesem Zweck wurde die elektrische Aktivität der Hirnrinde bei Katzen studiert, bei welchen der Hirnstamm im Gebiet der Brücke unmittelbar vor dem Austritt des Nervus trigeminus halb durchschnitten worden war. Diese Untersuchungen wurden im chronischen Experiment ausgeführt. Nach einer derartigen Halbdurchschneidung des Hirnstamms entwickelte sich in den beiden Hemisphären ein unsymmetrisches Hirnstrombild, wobei die *kontralaterale* Seite eine grössere Tendenz zur Synchronisierung aufwies als die ipsilaterale Hemisphäre, in welcher die Aktivität asynchron blieb. Die gleiche Asymmetrie des Elektroenzephalogramms bestand, wenn durch Halbdurchschneidung des Hirnstamms erzeugte akute Effekte bei der ''encéphale isolé'' Präparation untersucht wurden. Dasselbe galt für alle Halbdurchschneidungen von der prätrigeminalen Ebene kaudalwärts bis zum rostralen Teil der Medulla oblongata. Keine Asymmetrie des EEGs wurde gefunden mit Halbdurchschneidungen des Hirnstamms in Abschnitten der Medulla oblongata, welche kaudal zu ihrer mittleren Portion angelegt wurden. In Kontrollexperimenten wurde gezeigt, dass diese Asymmetrie sehr wahrscheinlich nicht auf einen irritierenden Effekt der Läsion auf das aufsteigende retikuläre System zurückzuführen ist, was an sich auch die ipsilaterale Asynchronie der Rindenaktivität erklären könnte. In ähnlichen Experimenten wurde festgestellt, dass die Asymmetrie des EEGs andauert, wenn der Karotissinus auf beiden Seiten denerviert oder der Nervus vagus beidseitig durchtrennt wird. Es wurde demnach bewiesen, dass der synchronisierende Effekt, welcher durch pressorezeptive, afferente Impulse ausgeübt wird, für das Zustandekommen der EEG-Asymmetrie nicht obligat ist.

Diese Befunde werden als gültiger Beweis für die Existenz eines vom kaudalen Teil des Hirnstamm ausgehenden ''synchronisierenden Mechanismus'' betrachtet. Bei halbseitiger Durchschneidung des Hirnstamms in der Brücke beeinflusst dieser Mechanismus die kontralateral zu dieser Läsion gelegene Hemisphäre durch Vermittlung der intakten Hälfte des Hirnstamms, währenddem auf der Seite der Hirnstammläsion die Vermittlung dieses Einflusses verunmöglicht wird. Infol-

gedessen entwickelt sich ein für Schlaf charakteristisches Hirnstrombild auf der Seite kontralateral zur Hirnstammläsion, währenddem die Rindenaktivität auf der ipsilateralen Seite vorwiegend asynchron verbleibt.

Die hypothetischen Eingenschaften dieses synchronisierenden Mechanismus werden im Lichte der gegenwärtigen Kenntnisse über die Regulierung der elektrischen Rindenaktivität bei der Katze besprochen.

The authors would like to express their deep gratitude to Professor G. Moruzzi for his constant advice and criticism during this experimental work and the preparation of this paper.

REFERENCES

BATINI, C., MORUZZI, G., PALESTINI, M., ROSSI, G. F. and ZANCHETTI, A. Persistent patterns of wakefulness in the pretrigeminal midpontine preparation. *Science*, **1958**, *128*: 30-32.

BATINI, C., MORUZZI, G., PALESTINI, M., ROSSI, G. F. and ZANCHETTI, A. Effects of complete pontine transections on the sleep-wakefulness rhythm: the midpontine pretrigeminal preparation. *Arch. ital. Biol.*, **1959**, *96*: 1-12.

BONVALLET, M., DELL, P. et HIEBEL, G. Tonus sympathique et activité électrique corticale. *EEG Clin. Neurophysiol.*, **1954**, *6*: 119-144.

CASPERS, H. Förderung und Hemmung von Narkoticawirkungen auf das Zentralnervensystem durch elektrische Stammhirnreizungen mit verschiedenen Reizgrössen. *Ztschr. ges. exper. med.*, **1955**, *125*: 386-400.

CASPERS, H. und WINKEL, K. Die Beeinflussung der Grosshirnrindenrhythmik durch Reizungen im Zwischen - und Mittelhirn bei der Ratte. *Pflügers Arch. ges. Physiol.*, **1954**, *259*: 334-356.

CORDEAU, J. P. and MANCIA, M. Effect of unilateral chronic lesions of the midbrain on the electrocortical activity of the cat. *Arch. ital. Biol.*, **1958**, *96*: 374-399.

DELL, P., BONVALLET, M. et HUGELIN, A. Tonus sympathique, adrénaline et contrôle réticulaire de la motricité spinale. *EEG Clin. Neurophysiol.*, **1954**, *6*: 599-618.

DOMINO, E. F. A pharmacological analysis of the functional relationship between the brain stem arousal and diffuse thalamic projection systems. *J. Pharmacol.*, **1955**, *115*: 449-463.

HESS, W. R. *Das Zwischenhirn. Syndrome, Lokalazationen, Funktionen.* Benno Schwabe and Co., Basel, **1949**, 187 pp.

HESS, R. JR., KOELLA, W. P. and AKERT, K. Cortical and subcortical recordings in natural and artificially induced sleep in cats. *EEG Clin. Neurophysiol.*, **1953**, *5*: 75-90.

HUGELIN, A. et BONVALLET, M. Tonus cortical et contrôle de la facilitation motrice d'origine réticulaire. *J. Physiologie*, **1957**a, *49*: 1171-1200.

HUGELIN, A. et BONVALLET, M. Etude expérimentale des interrelations réticulo-corticales. Proposition d'une théorie de l'asservissement réticulaire à un système diffus cortical. *J. Physiologie*, **1957**b, *49*: 1201-1223.

HUGELIN, A. et BONVALLET, M. Analyse des postdécharges réticulaires et corticales engendrées par des stimulations réticulaires. *J. Physiologie*, **1957**c, *49*: 1225-1234.

INGVAR, D. H. and SÖDERBERG, G. U. Cortical blood flow related to EEG patterns evoked by stimulation of the brain stem. *Acta physiol. scand.*, **1958**, *42*: 130-143.

KNOTT, J. R., INGRAM, W. R. and CHILES, W. D. Effects of subcortical lesions on cortical electroencephalogram in cats. *Arch. Neurol. Psychiatr.* Chicago, **1955**, *73*: 203-217.

MACHNE, X., CALMA, I. and MAGOUN, H. W. Unit activity of central cephalic brain stem in EEG arousal. *J. Neurophysiol.*, **1955**, *18*: 547-558.

MAGNI, F., MORUZZI, G., ROSSI, G. F. and ZANCHETTI, A. EEG arousal by selective injection of barbiturate into the lower brain stem circulation. *Arch. ital. Biol.*, **1959**, *97*: 33-46.

MAGOUN, H. W. and RHINES, R. An inhibitory mechanism in the bulbar reticular formation. *J. Neurophysiol.*, **1946**, *9*: 165-171.

MAZZELLA, H., GARCÍA MULLIN, R. and GARCÍA AUSTT, E. Effect of carotid sinus stimulation on the EEG. *Acta Neurol. latinoamer.*, **1957**, *3*: 361-364.

MORUZZI, G. Spontaneous and evoked electrical activity in the brain stem reticular formation. *Abstr. Rev. XX int. Physiol. Congr.*, Bruxelles, **1956**, 269-286.

MORUZZI, G. and MAGOUN, H. W. Brain stem reticular formation and activation of the EEG. *EEG Clin. Neurophysiol.*, **1949**, *1*: 455-473.

PROCTOR, L. D., KNIGHTON, R. S. and CHURCHILL, J. A. Variations in consciousness produced by stimulating reticular formation of the monkey. *Neurology*, **1957**, *7*: 193-203.

ROSSI, G. F. and ZANCHETTI, A. The brain stem reticular formation. Anatomy and physiology. *Arch. ital. Biol.*, **1957**, *95*: 199-435.

ROTHBALLER, A. B. Studies on the adrenaline-sensitive component of the reticular activating system. *EEG Clin. Neurophysiol.*, **1956**, *8*: 603-621.

Reference: CORDEAU, J. P. and MANCIA, M. Evidence for the existence of an electroencephalographic synchronization mechanism originating in the lower brain stem. *EEG Clin. Neurophysiol.*, **1959**, *11*: 551-564.

CLINICAL AND LABORATORY NOTES

Edited by R. S. SCHWAB, M.B. and H. FISCHGOLD, M.D.

EPILEPSY IN CONJOINED SIAMESE TWINS

IAN HAY BROWN, M.D.
Miami Valley Hospital, Dayton, Ohio

(Received for publication: June 26, 1958)

INTRODUCTION

Conjoined twins were first described in the year 375 A.D. There were many notable cases from that time on, but the term "Siamese twins" became popularized following the appearances of Chang and Eng (1811-1874) in the Barnum Circus in this country (Luckhardt 1941). The incidence of Siamese twins is difficult to estimate, but in larger cities there have been reports of these births occurring in approximately every 60,000 to 80,000 deliveries (Mortimer *et al.* 1951, 1952; Potter 1952), while it has been estimated that world wide there is probably an incidence of survival of about one in every 2 million births (Aird 1954, 1955). The interest in Siamese twins in the past has been mainly obstetrical and anatomical, but more recently surgeons have been attempting to separate them with varying success (e.g. Aird 1955; Grossman *et al.* 1953; Holgate *et al.* 1956; Spencer 1956; Wilson *et al.* 1957). In spite of all modern advances, the total number of survivals is small and it is believed that at this time there are only four sets of conjoined twins alive in the U. S. A.

In the history of Dayton, Ohio, there have been four sets of Siamese twins delivered but the first survivors were Ronnie and Donnie G. who were born on October 28, 1951. Although twins had been anticipated, the practitioner had considerable difficulty with the delivery. The head and shoulders of the first twin were easily delivered but when the trunk failed to exit, the doctor suspected that the umbilical cord had twisted round the body and in attempting to correct this he discovered that the reason for the delay was the fusion of the two trunks. Eventually the doctor was able to obtain a successful but belated delivery. The infants were in no apparent distress and weighed a total of 11¾ lbs. In their early development there were no major difficulties. As can be seen from the photographs (fig. 1), the twins are thoracopagus, being joined below the xiphisternum. They have independent sets of all upper organs, including heart, liver, etc., but they share a common lower bowel and have a rudimentary urogenital apparatus and anus which is essentially a cloaca (fig. 2, 3). As is so often the case with Siamese twins, Ronnie and Donnie were not quite symmetrical or identical and in earlier years Donnie was the larger twin and the initiator of most of their activities, mentally and physically. However, in the past few years the roles have been reversed and Ronnie is now the larger and the leader. In walking the twins can move in the conventional way, but are more proficient when moving laterally. For increased speed they have developed a technique whereby, in

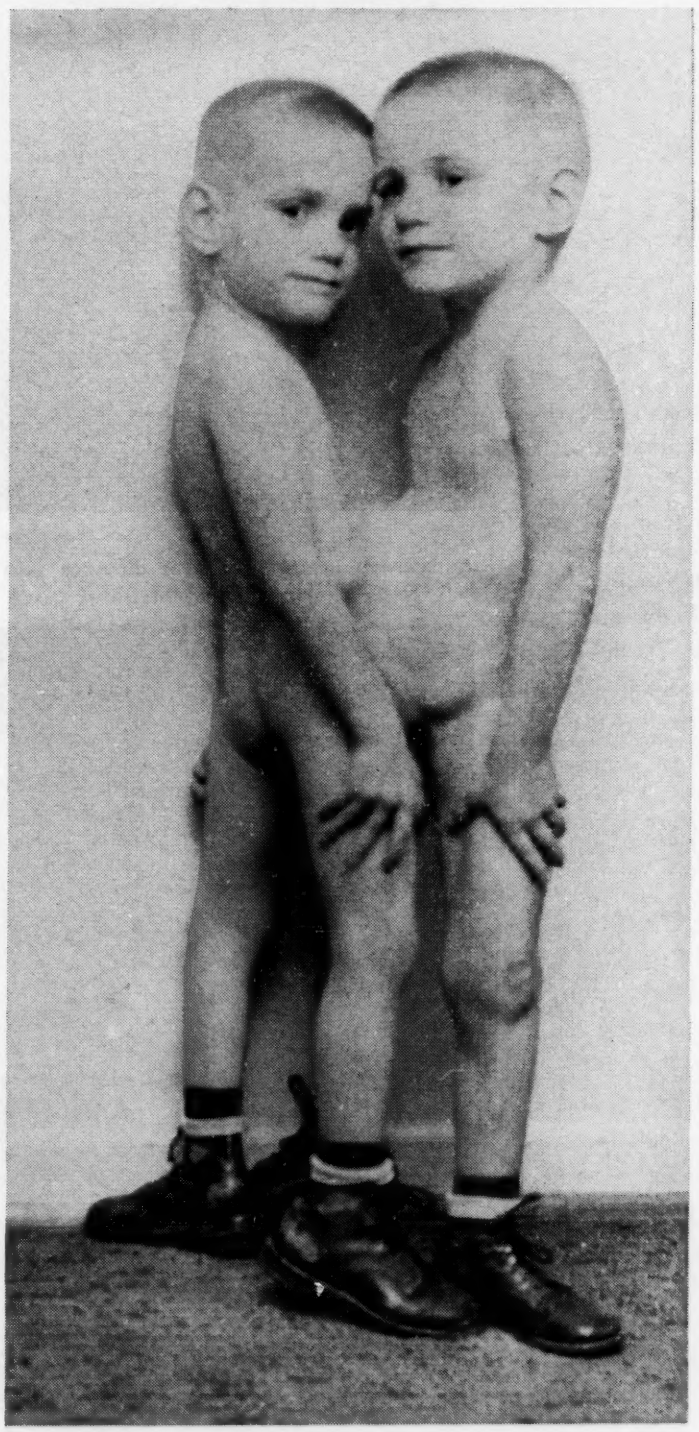


Fig. 1
Early photograph of the twins illustrating the area of fusion.

effect, Ronnie carries Donnie and only one set of legs is used.

The twins were well until February, 1957, when Ronnie developed a high fever which lasted a few days. Two months later a similar febrile episode occurred, but as the twins were in circuit with a carnival, no diagnosis was made in either instance and treatment was non-specific. These illnesses did reveal, however, the physiologic independence of the twins for Donnie was completely unaffected while Ronnie

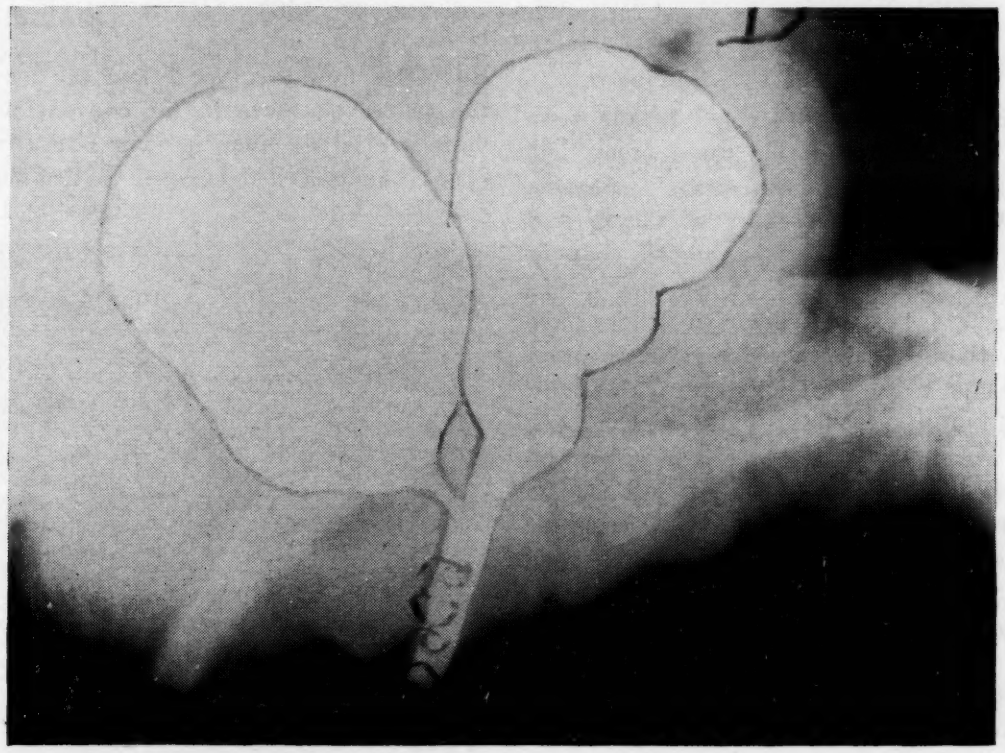


Fig. 2
A catheter inserted a short distance into the cloaca enables dye to fill the common urethra and separate bladders.

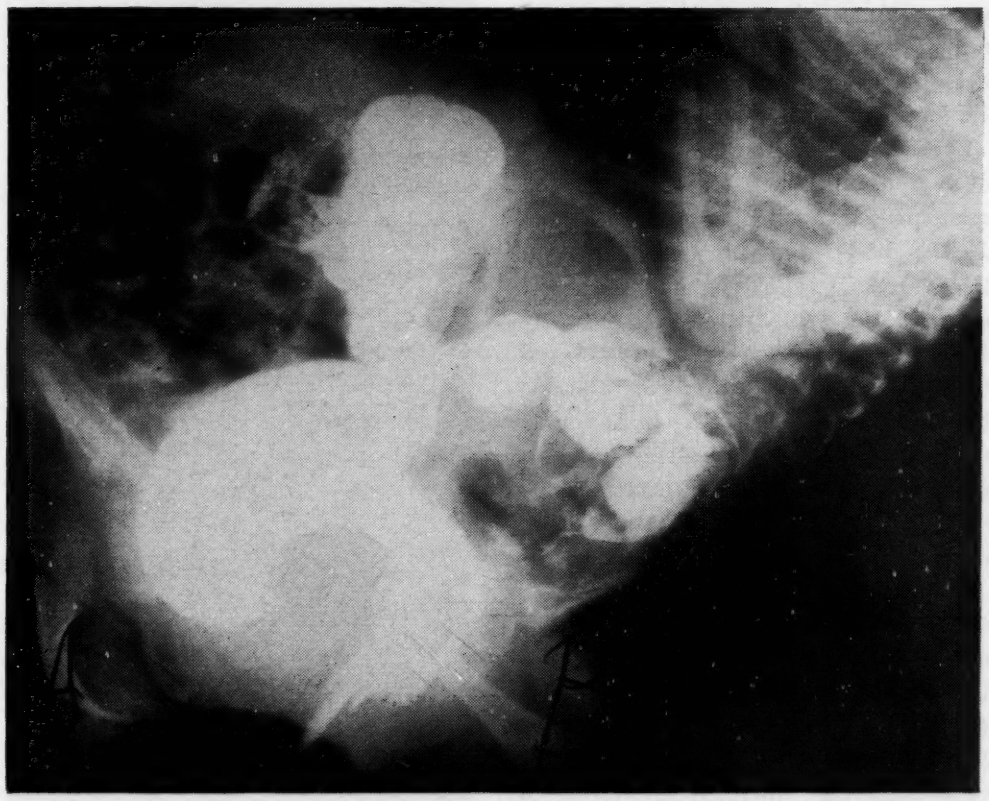


Fig. 3
The same catheter as in figure 2 inserted further into the cloaca allows the common rectum to be filled. The separation into 2 transverse colons can be seen.

was febrile and sick. In June, 1957, Ronnie began to have what were first believed to be "cramps" of the left leg at which time the leg was slightly raised from the ground and appeared "stiff". The "cramps" lasted only a few seconds at a time but even so were embarrassing as they usually occurred in periods of excitement when Ronnie was running and as a consequence he would fall on top of Donnie. As weeks went by, it was noted that Ronnie's left arm was becoming involved with these cramps, and later the picture included head-turning to the left, usually a fixed stare, which rarely was also to the left. In the course of the travelling around, no definitive diagnosis was made until the twins reached Arkansas where the diagnosis of epilepsy was considered and the twins were recommended to return home for an evaluation of this possibility. The physician who had brought the twins into the world some six years previously referred them to the EEG Department of Miami Valley Hospital in November, 1957, for study. On closer questioning of the parents, it was revealed that "shaking" had occurred very rarely during the night and had been heard but mistaken for nightmares.

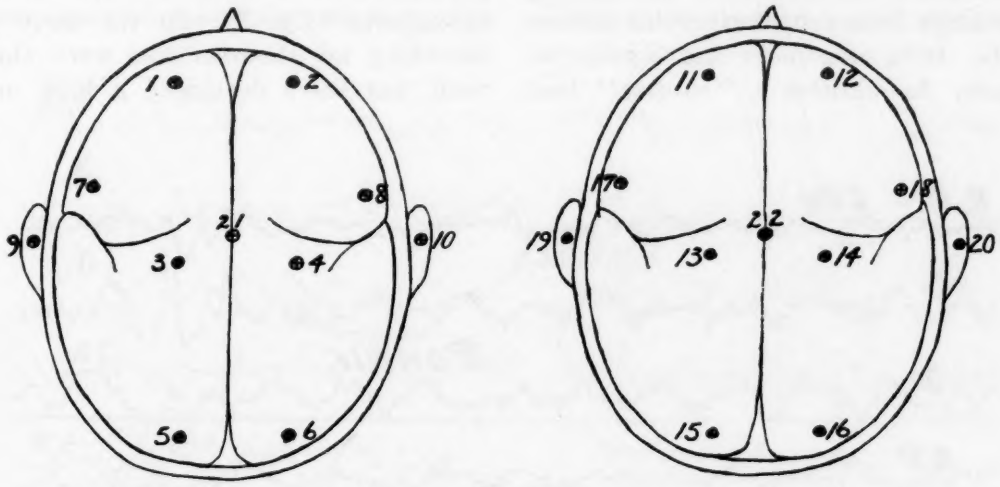


Fig. 4
Electrode placements.

TECHNIQUE

With the unusual assignment given us, some careful planning was obviously necessary. It was decided that in so far as the history was not too clear, and because of the uniqueness of the situation, a

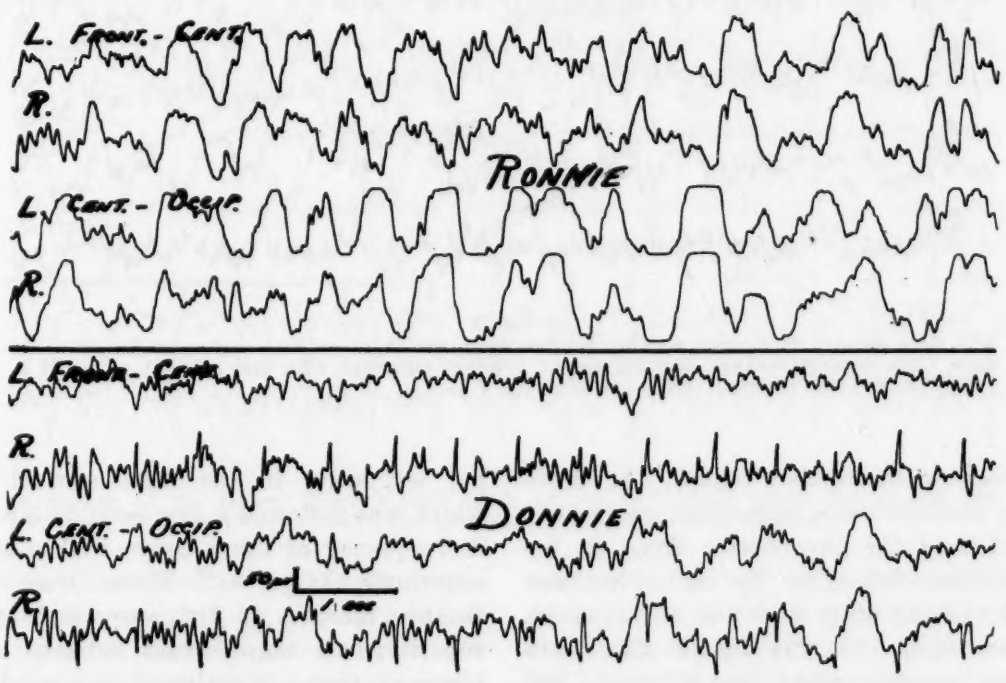


Fig. 5
Simultaneous recordings on the twins showing different phases of sleep. Note also the prominent EKG artefact in R. Cent. lead of Donnie.

simultaneous recording from the two brains was most desirable. Silver cup electrodes (of the type supplied by the Grass Instrument Company) were affixed with bentonite over the frontal, central, occipital and anterior-temporal areas. An electrode was placed on the vertex and also one on each ear (fig. 4). An 8-channel Grass console was employed for making simultaneous recordings from four comparable derivations on each twin. Both monopolar and bipolar recordings were made. In addition a "cardiac" lead was added to each intrascapular region, the more desirable anterior position being impossible on account of the juxtaposition of the two chests. Even so, because of the positions taken up by the twins, one lying on his back and the other over him on his chest, the task was not easy. It was hoped that both waking and sleep records could be obtained, but the former became impossible as the boys constantly fought and rolled over each other on the bed so that Seconal ® had to be administered.

RESULTS

Before the recording actually began the physiologic independence of the twins was illustrated by the fact that one became asleep some 10 min. before, and in spite of, the other. The first pages of recording revealed totally different phases of sleep pattern for each twin and the difference remained throughout (fig. 5). In the early portions of the recording no abnormalities were observed in either twin, but there developed a high amplitude slow 4 per sec. wave in the right central lead of Ronnie which was followed a few seconds later by an increase in frequency of these waves with a spread essentially anteriorly (fig. 6). These were followed by a further increase in frequency and spread, and when superimposed muscle fast activity appeared it was observed that a right-sided clonic seizure was in progress involving the leg predominately, but the arm as well, lasting about 50 sec. In a much later portion of the record spike discharges were observed in the

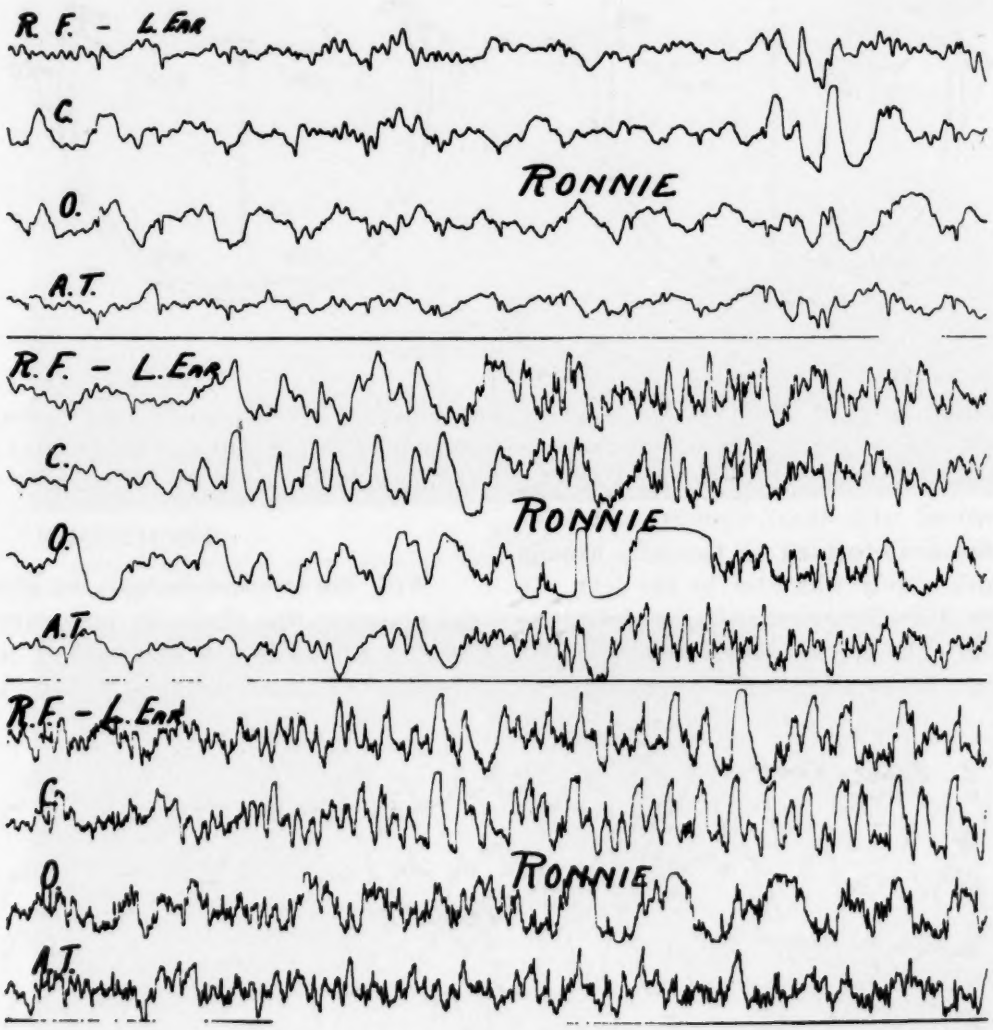


Fig. 6
The first 30 sec. of seizure activity beginning in the right central region of the affected twin. The muscle tension and movement artefact coincide with the clinical onset of a right-sided clonic seizure. (Same scale as fig. 7.)

right central region with a slight reflection to the left central region but with no spread to the remaining right-sided leads. Throughout no abnormalities were noted in the record of Donnie (fig. 7).

The EKG riddle seemed to be solved rather early in the recording for EKG artefact could be detected in the monopolar recordings of both Ronnie and Donnie and it was observed that these artefacts were synchronous. Using the "cardiac" leads the same results seemed to be the case, but by a lucky accident when the scalp leads of Ronnie were run to the vertex of Donnie two distinguishable rhythms could be identified and these were quite asynchronous, one around 90 beats/min. and the other around 83/min. (fig. 8).

DISCUSSION

With the exception of the case of the craniopagus Brodie twins (Durr 1952; Grossman *et al.* 1953; Sugar 1953), the data here presented are believed to be the first electroencephalographic recordings of epilepsy in Siamese twins. It is also of interest from the purely epileptic viewpoint that the seizure history indicated the earliest manifestations as tonic movements of the left leg, spreading in the course of development to other portions of the left side and finally revealing right-sided clonic seizures. The only EEG manifestations of seizure activity have been confined to the right central region even when the patient was having a clonic seizure on the ipsilateral side. This phenomenon has been seen by us previously in

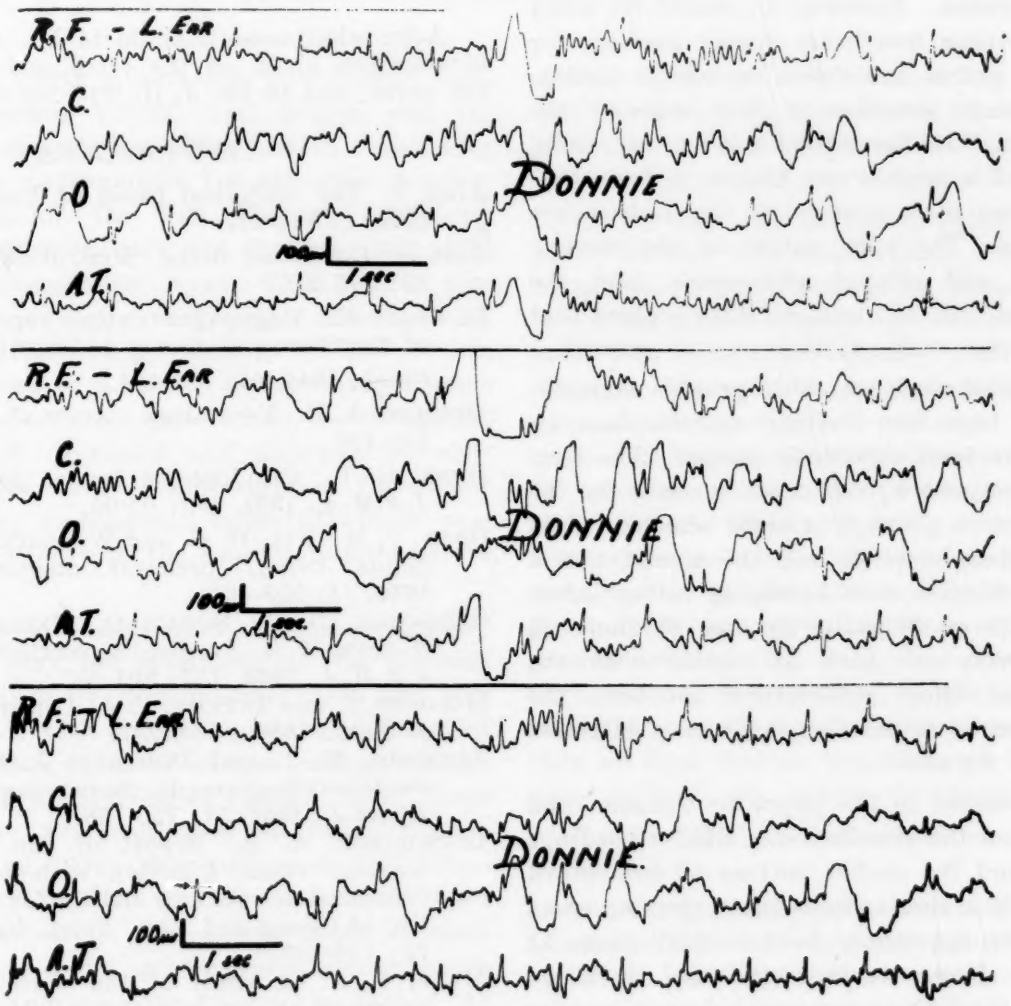


Fig. 7

Simultaneous record of the unaffected twin during the same 30 sec. period as illustrated in figure 6.

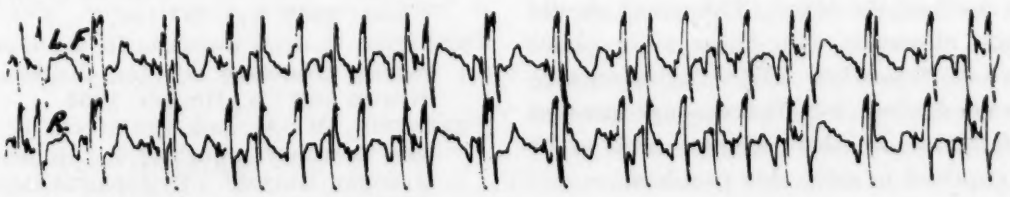


Fig. 8

A section of the record where frontal leads of one twin were being run against the vertex of the other twin, revealing independent asynchronous EKG artefacts.

a few cases, and of course reported by others (e.g. Penfield and Jasper 1954). The present EEG disturbance coincides very well with the earliest clinical manifestations of the seizure pattern, and this point has been clearly emphasized as being the most important by Penfield. The etiology is a matter of conjecture at the present time although it seems likely that some birth trauma and/or anoxia occurred and that the febrile episodes early in 1957 triggered off the seizure mechanism. However, it should be noted that there is a strong hereditary factor present, for although neither parent has shown convulsive tendencies, there are many members of both sides of the family who have. On the father's side, an uncle, female cousin and a nephew are known to have convulsions, while two male cousins of the mother are similarly affected. The very nature of the electroencephalographic and clinical phenomena, and the involvement in only one of identical twins suggest that heredity is not the main etiologic agent present.

Since the original electroencephalographic examination there have been two further examinations on Ronnie which have been essentially normal. The first of these was prompted by an acute increase in the number of seizures to about 10 a night when the child was placed on phenobarbital, and the second was a follow up after seizures were becoming rather infrequent as a result of Dilantin ® and Tridione ® therapy. The twins are back on circuit with the carnival now and latest information indicates the latter combination of medication is proving effective in controlling the seizures.

We were interested in the paper by Johnson and Doherty (1957) on the simultaneous EKG recordings on their twins, and the earlier portion of our record seemed to indicate a similarity between the two cases in that the hearts apparently beat in both cases at the same rates. However, the accidental detection of asynchronous rhythms in our case led us to wonder if we in our early observation and Johnson *et al.* in their case were actually recording impulses from one heart through the chest of the other. This point should be noted by future observers who know more about cardiology than we profess when EKG studies on conjoined twins are conducted, but thoracopagi present considerable difficulties in this respect and much ingenuity will be required to solve this problem.

SUMMARY

The history is presented of conjoined Siamese twins, one of whom has developed epileptic seizures. The EEG simultaneous recordings of the twins and a clinical seizure of one twin are presented and discussed. The chances of directly recording a seizure in an epileptic conjoined twin is estimated as being in the neighborhood of one in 500 million. No attempt has been made in this report to discuss the general problem of conjoined twinning, theories of development, etc., for which adequate references exist (Aird 1954, 1955; Dawson 1944; Dunbar 1934; Gray *et al.* 1950; Luckhardt 1941; Mall 1908; Mortimer *et al.* 1942; Perlstein *et al.* 1927; Potter 1952).

Acknowledgment is made to Dr. A. Kuhr for the information given on the birth and development of the twins, and to Dr. J. G. Tye for copies of X-rays.

REFERENCES

AIRD, I. The conjoined twins of Kano. *Brit. M. J.*, **1954**, *1*: 831-837.

AIRD, I. Conjoined twins. *Med. World*, London, **1955**, *83*: 217-221.

DAWSON, H. Pygopagus twins; report of dissection of the thorax, abdomen and pelvis. *Amer. J. Dis. Child.*, **1944**, *68*: 395-404.

DUNBAR, A. E. Teratology. *Amer. J. Surg.*, **1934**, *24*: 152-158.

DURR, S. P. Craniopagus twins; report of a case. *J.A.M.A.*, **1952**, *150*: 93-95.

GRAY, C. M., NIX, H. G. and WALLACE, A. J. Thoracopagus twins; prenatal diagnosis. *Radiology*, **1950**, *54*: 398-400.

GROSSMAN, H. J., SUGAR, O., GREELEY, P. W. and SADOVE, M. S. Surgical separation in craniopagus. *J.A.M.A.*, **1953**, *153*: 201-207.

HOLGATE, J. and IKPEME, B. J. Conjoined twins. *Brit. J. Surg.*, **1956**, *43*: 626-7.

JOHNSON, N. J. and DOHERTY, J. E. Simultaneous electrocardiograms in thoracopagus twins. *Amer. Heart J.*, **1957**, *53*: 150-156.

LUCKHARDT, A. B. Report of the autopsy of the Siamese twins together with other interesting information covering their life; a sketch of the life of Chang and Eng. *Surg., Gynec. Obst.*, **1941**, *72*: 116-125.

MALL, F. P. A study of the causes underlying the origin of human monsters. *J. Morphol.*, **1908**, *19*: 3-368.

MORTIMER, B. and KIRSHBAUM, J. D. Human double monster (so-called Siamese twins). *Amer. J. Dis. Child.*, **1942**, *64*: 697-704.

PENFIELD, W. and JASPER, H. *Epilepsy and the functional Anatomy of the Human Brain.* Little, Brown and Co., Boston, **1954**.

PERLSTEIN, M. A. and LECOUNT, E. R. The history and necropsy report of the Bohemian twins, Rosa-Josepha Blazek. (Pygopagus twins.) *Arch. Path.*, **1927**, *3*: 171-192.

POTTER, E. L. *Pathology of the Foetus and the Newborn. Publishers*, **1952**.

SUGAR, O. The Brodie craniopagus twins. *Trans. Amer. Neur. Assoc.*, 78th Meeting, **1953**, P. 198-9.

WILSON, H. and STORER, E. H. Surgery in "Siamese" twins: a report of three sets of conjoined twins treated surgically. *Ann. Surg.*, **1957**, *145*: 718-725.

Reference: BROWN, I. H. Epilepsy in conjoined siamese twins. *EEG Clin. Neurophysiol.*, **1959**, *11*: 565-570.

PRINTED IN CANADA

TRANSIENT ELECTROENCEPHALOGRAPHIC PATTERN CHARACTERISTIC OF SUB-ACUTE LEUCO-ENCEPHALITIS IN A CASE OF ACUTE HEAD INJURY

ROBERTO ZAPPOLI, M.D.

Clinica Delle Malattie Nervose e Mentali Dell'Universita'di Padova, Padua, Italy

(Received for publication: August 4, 1958)

Radermecker (1949), Cobb and Hill (1950), Gozzano and co-workers (1950) and Martin and co-workers (1950) described an EEG pattern, which they considered to be pathognomic for sub-acute progressive encephalitis of the Van Bogaert (sub-acute sclerosing leuco-encephalitis) and Dawson (sub-acute inclusion body encephalitis) type. This pattern consists of periodic, brief, synchronous bursts of irregular slow waves of high amplitude. The bursts, generally composed of a rather rapid, biphasic wave followed by two or three slow waves, occur against a background of depressed and disorganized slow activity. Complex motor manifestations (myoclonic or choreo-athetoid movements) appeared almost constantly in association with the slow-wave outbursts in the EEG.

Most authors have confirmed these observations; some, however, deny the specificity of the periodic discharges described by Radermecker, Cobb and Hill *et al.*, having met with an EEG pattern of identical appearance in other forms of diffuse encephalopathy with a wide variety of etiologies (Maleci 1951; Jones and Nevin 1954; Alajouanine *et al.* 1955; Terzian 1955; Vizioli *et al.* 1955; Morocutti *et al.* 1957; Sanguineti *et al.* 1952-1958; Pinelli *et al.* 1955-1958; Lesse *et al.* 1958; etc.). The greater part of these cases were affected by severe sub-acute infantile encephalopathies; in some the total regression of the clinical symptomatology and the return to normality of the EEG records was observed.

A case of acute head injury that presented a regular recurrence of brief, synchronous slow-wave bursts on EEG, with complete recovery, is here reported.

CASE REPORT

M. G. F. Male, aged 26. Severe head injury sustained in car accident. On admission patient in rather deep coma, having completely lost touch with surroundings. Light hyperthermia; blood-pressure, pulse rate and respiration almost normal. Tendon, corneal and pupillary reflexes symmetrically somewhat diminished. Light diffuse muscular hypotonia. Patient moved all limbs in response to pain. No ''decerebrate attacks'' or other abnormal movements observed. X-ray of skull showed thin vertical fracture line (about 4 cm.) on left side of occipital bone. No clinical evidence of intracranial haematomata, raised intracranial pressure or cerebral oedema.

On the day after admission patient still practically out of contact with environment; almost unresponsive to various auditory and startle stimuli but responded to painful stimuli applied anywhere in the body. EEG then (32 hrs. after accident) showed periodic synchronous slow-wave bursts against background of depressed and disorganized activity. The burst, composed of a rather rapid biphasic wave followed by one or two high voltage slow waves, recurred regularly every 7-8 sec. Passive opening and shutting of eyelids, various painful, startle and photic stimuli, single and rhythmical, did not modify the periodicity of these discharges or in any way influence the background activity (fig. 1, A, B). The periodic bursts were not in any relation to the cardio-respiratory modifications. The recording was continued for more than an hour, but no variations of the EEG pattern were noticed. No abnormal movements observed.

Cerebrospinal fluid of normal composition, slightly hypertensive.

Patient gradually more alert and three days after admission able to recognize relatives, obey simple commands and hold a brief conversation, asking and answering simple questions. At times however drowsy, very confused, disoriented and restless. That day second record still very disorganized and flat, in all leads irregular slow waves (4-7 c/sec.) of low voltage prevailing; in posterior regions rhythm 6-8 c/sec. visible (fig. 1; C). Such abnormal activity very little influenced by opening and shutting of eyes and by acoustic stimuli. Slow-wave discharges no longer observed.

On following days improvement progressive and rapid. By fourteenth hospital day patient symptom-free. He only complained sometimes of a slight headache and had a prolonged (2-3 days), retro- anterograde amnesia. EEG consisted of 10 c/sec. rhythm of low voltage prevalent in posterior leads, regularly blocked by opening of eyes (fig. 2, A); hyperpnoea provoked somewhat marked slowing of cerebral bioelectrical activity.

Patient discharged after a fortnight. A month after accident record quite normal (fig. 2, B) and a year later no trouble noticed.

COMMENT

The favourable clinical progress ending in complete recovery, the diffuse symmetrical alterations and the successive return to normality of the EEG, showed flat and disorganized tracings. In the first EEG no arousal reactions or any other changes to external stimuli were visible.

Diffuse and symmetrical abnormalities and especially EEG unresponsiveness to various stimuli are almost constant phenomena, carefully studied by Fischgold (1953, 1957), in post-traumatic comas with brain-stem damage, particularly if deep enough. The

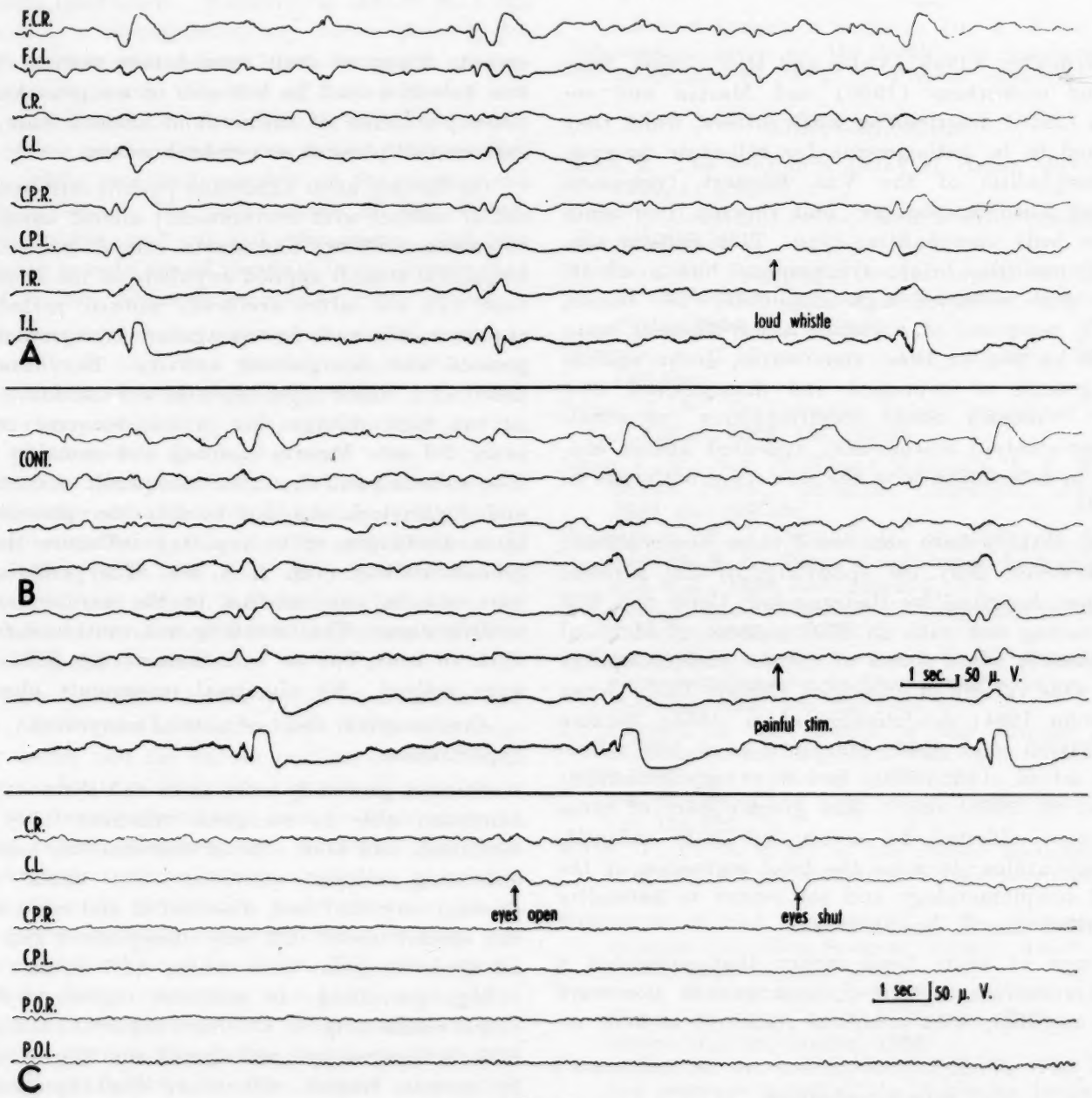


Fig. 1

L = left; R = right; F = frontal; C = central; P = parietal; O = occipital; T = temporal. Explanation in text.

induce us to suppose that in this case the rather deep and prolonged post-traumatic coma was caused by an uncomplicated and not very severe brain contusion. Periodically recurring slow-wave bursts against a background of depressed activity, were observed in the first EEG (32 hrs after accident), not however in the second, recorded on the third hospital day, which absence of EEG reactivity seems to have considerable importance in indicating the depth of the unconscious state and to be useful for the prognosis, being generally considered a sign of irreversible coma. It is important to remark that in sub-acute, progressive leuco-encephalitis and in the diffuse encephalopathies with similar EEG patterns that have been described,

arousal stimuli are generally without significant effect.

EEG flattening, so-called ''post-traumatic general suppression'' is common in the days immediately following acute head-injuries but does not appear to have any particular diagnostic and prognostic significance (Fischgold *et al.* 1946; De Vlieger 1958; De Stoppelaar *et al* 1958; etc.).

On the contrary, periodic, brief slow-wave bursts, considered by the greater part of the authors as specific of sub-acute leuco-encephalitis with or without inclusion bodies, do not seem to us ever to have been observed in cases of post-traumatic coma. Only Fischgold (1957) alludes to the possible appearance in slight post-traumatic coma of periodical discharges of slow-wave activity at sufficiently regular intervals, often corresponding to cardio-respiratory modifications. In our case very interesting also was the complete and rapid regression of these unusual EEG abnormalities, which were not accompanied by any particular motory manifestations.

The problem of periodic EEG phenomena in human pathology is very complex, so much so that their appearance is habitually met with in electroencephalography, above all in physiologic conditions, as for instance in sleep. Firstly, it must be noted that periodic phenomena are manifested only in particularly grave pathological states and are the expression of a deep disorganization of the cerebral electro-genesis. In order to explain this tendency to periodicity of cerebral biorhythms in conditions so different one to another as obtained in sleep and in severe diffuse encephalopathies of various etiology, numerous interpretative hypotheses have been proposed (Pampiglione *et al.* 1953; Kirstein 1954; Terzian, 1955; Vizioli *et al.* 1955; Andreani *et al.* 1955; Radermecker 1956; Morocutti *et al.* 1957; Lesse *et al.* 1958).

Particularly worthy of consideration are the views of Terzian (1955), who is of the opinion that pathologic periodic phenomena are brought about by those abnormal situations that determine the more or less complete isolation of the cerebrum from external stimuli. The appearance of the periodic discharges on EEG would in this case be directly in relation with the site of the gravest lesions, especially of those localized in the brain-stem and in the cerebral white matter. These lesions, that cause the transitory or progressive isolation of the cerebral grey structures, release their intrinsic bio-electrical periodicity, in particular that of the cortex, which in normal conditions is disorganized by the continual afferent impulses evolving right through the brain-stem forma-

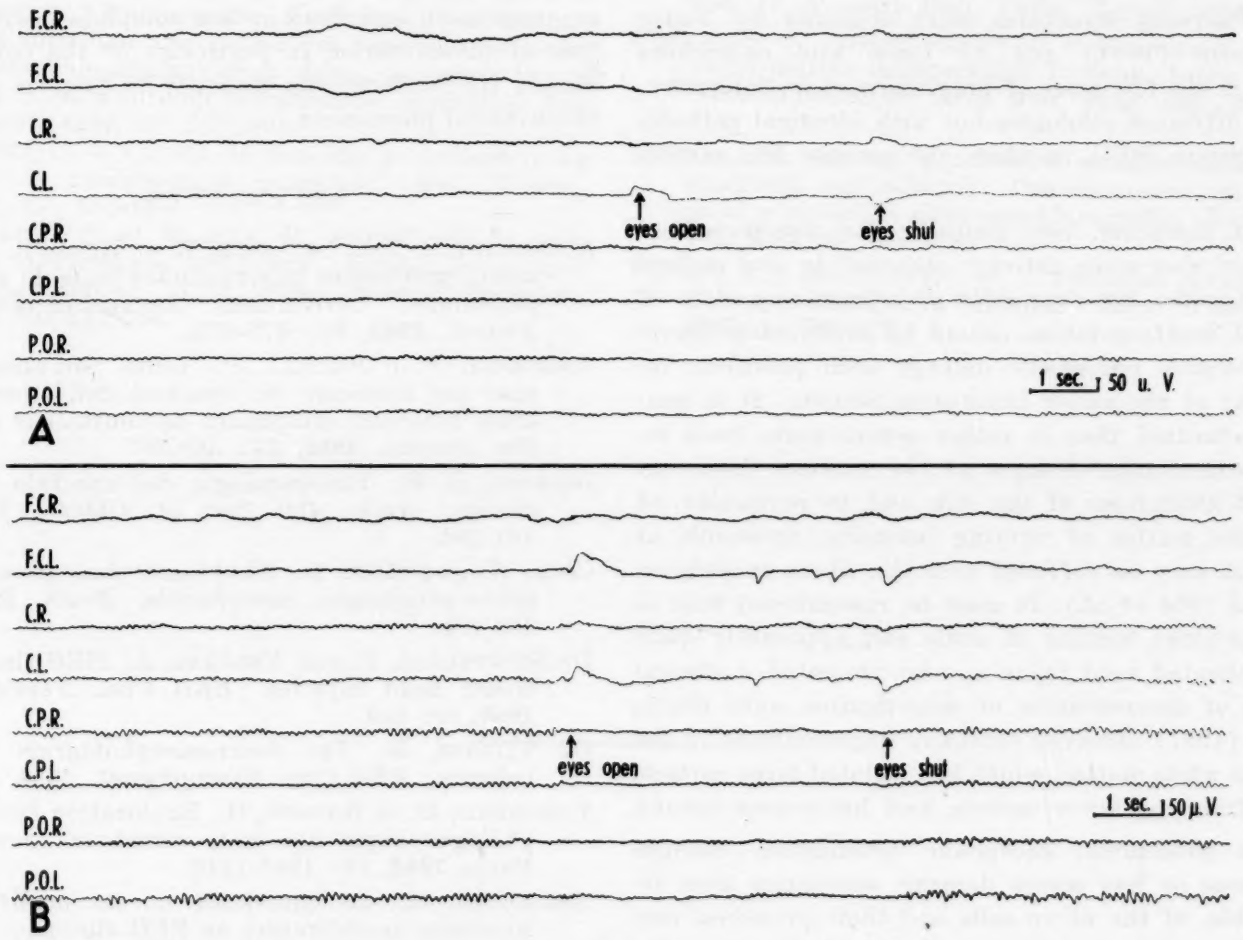


Fig. 2

tions (brain-stem activating system). The EEG unresponsiveness to the various arousal stimuli in such conditions may be explained in this way.

It is known that in sub-acute, progressive leuco-encephalitis, with or without inclusion bodies, of which the periodic slow-wave bursts on EEG are one of the characteristics, the gravest alterations are observed in the cerebral white matter; diffused and more or less marked lesions are also met with in the cortex, basal ganglia and brain-stem structures. To these important lesions, symptoms of progressive decerebration or decortication tipical of sub-acute leuco-encephalitis have been attributed by the greater part of the authors. Diffuse, severe alterations of the same central nervous structures were observed by Jones and Nevin (1954) and by Lesse and co-workers (1958) in the few cases of progressive encephalopathy, having different etiologies but with identical periodic discharges on EEG, in which the autopsy was carried out.

It is, therefore, very probable that the periodical bursts of slow-wave activity observed in our patient were, they too, the expression of a transitory state of cerebral deafferentation caused by sufficiently severe but reversible encephalic damage with prevalent involvment of the upper brain-stem centres. It is generally admitted that in rather severe acute head injuries oedematous changes of the nervous tissue set in, with alterations of the cells and, in particular, of the white matter of varying intensity, reversible or not, that may be diffused over the whole encephalon (Belloni 1954 *et al.*). It must be remembered that in some patients, victims of acute and apparently quite uncomplicated head injuries, who presented a clinical picture of decerebration or decortication until death, Strich (1957) observed extensive degenerations of the cerebral white matter, which had isolated large cortical areas from the lower centres, and brain-stem lesions.

The widespread encephalic oedematous changes with more or less severe damage, sometimes even irreversible, of the nerve cells and their branches, presumably explain the dynamic bio-electrical state in the days immediately following the acute head injuries, which often varied from hour to hour and from day to day. In fact the most different EEG patterns, often continually mutable and in direct dependence of the prevailing impairment of one or the other encephalic structure, are to be met with at this stage.

This EEG pattern, considered characteristic for sub-acute leuco-encephalitis with or without inclusion bodies, was observed by some authors also in other forms of diffuse encephalopathies, sometimes with favourable course, with a wide variety of etiologies.

We are therefore of the opinion that this type of EEG pattern is not specific for a certain morbous condition but that it is indicative of diffuse encephalic damage with structural changes of the nervous tissue of varying severity, with prevalent impairment of the cerebral white matter and of the brain-stem structures, which may be transient or permanent and unspecific as to etiology. These alterations would bring about a condition of reversible or progressive and more or less complete deafferentation of the cerebrum in particular of the cortex, releasing its characteristic tendency to produce periodic bioelectrical phenomena.

SUMMARY AND CONCLUSIONS

A case of post-traumatic coma that presented on the first EEG, recorded 32 hrs. after the accident, a regular recurrence of brief, synchronous slow-wave bursts against a background of depressed activity, with complete recovery, is reported.

REFERENCES

ALAJOUANINE, TH., LECASBLE, R. et REMOND, A. Eléments graphiques paroxystiques lents de survenue périodique. Corrélations électrocliniques. *Rev. Neurol.*, **1955**, *93*: 477-478.

ANDREANI, F. e PINELLI, P. Delta periodico in un caso con sindrome da trombosi dell'arteria cerebrale anteriore complicata da confusione mentale. *Riv. Neurol.*, **1955**, *25*: 589-597.

BELLONI, G. B. Fisiopatologia dell'encefalo traumatizzato. *Arch. Atti Soc. It. Chirur.*, **1954**, *1*: 161-182.

COBB, W. and HILL, D. Electroencephalogram in subacute progressive encephalitis. *Brain*, **1950**, *73*: 392-404.

DE STOPPELAAR, F. and VERJAAL, A. EEG-findings in closed head injuries. *EEG Clin. Neurophysiol.*, **1958**, *10*: 204.

DE VLIEGER, M. The electroencephalogram in head injuries. *EEG Clin. Neurophysiol.*, **1958**, *10*: 204.

FISCHGOLD, H. et BOUNES, G. Exploration électroencéphalographique des états comateux. *Sem. Hôp.*, Paris, **1946**, *22*: 1245-1246.

FISCHGOLD, H. La conscience et ses modifications. Systèmes de références en EEG clinique. I. Cong. Inter. Scien. Neurol., Bruxelles, *Acta Med. Belg.*, **1957**, *2*: 181-213.

GOZZANO, M., MENGOLI, G. E SCHIAVI, E. Studio elettroencefalografico di un caso di leucoencefalite subacuta sclerosante. *Arch. Psicol. Neurol. Psichiat.*, **1950**, *2*: 325-334.

JONES, D. P. and NEVIN, S. Subacute cortical degeneration with myoclonus and epilepsy. *Trans. Amer. Neurol. Ass.*, **1954**, *79*: 144-146.

JONES, D. P. and NEVIN, S. Rapidly progressive cerebral degeneration (subacute vascular encephalopathy) with mental disorders, focal disturbances and myoclonic epilepsy. *J. Neurol. Neurosurg. Psychiatr.*, **1954**, *17*: 148-159.

KIRSTEIN, L. Suppression-burst activity during sleep. Report of a case of transient cerebral disorder. *EEG Clin. Neurophysiol.*, **1954**, *6*: 671-673.

LAIRY-BOUNES, G. C. et FISCHGOLD, H. Réaction EEG diffuses aux stimulations psycho-sensorielles: intérêt clinique. *EEG. Clin. Neurophysiol.*, **1953**, *5*: 343-362.

LESSE, S., HOEFFER, F. A. and AUSTIN, J. H. The electroencephalogram in diffuse encephalopathies. *Arch. Neurol. Psychiat.*, Chicago, **1958**, *79*: 359-375.

MALECI, O. Quadro elettroencefalografico di un caso di encefalite sclerosante subacuta. *Riv. Neurol.*, **1951**, *21*: 378-383.

MARTIN, F., MACKEN, J. et HESS, R. Sur une encéphalite subaiguë ayant les caractères de la leucoencéphalite sclérosante avec inclusions. Etude anatomo-clinique, biologique et électroencéphalographique de la première observation suisse. *Arch. Suiss. Neurol. Psychiat.*, **1950**, *66*: 217-260.

MOROCUTTI, C., MACCAGNANI, F., SINISI, C. E VIZIOLI, R. Contributo allo studio dei fenomeni periodici in elettroencefalografia; delta periodico in un caso di encefalite da toxoplasmosi neonatale. *Riv. Neurol.*, **1957**, *27*: 201-209.

MOROCUTTI, C., E VIZIOLI, R. Scariche periodiche in un caso di toxoplasmosi neonatale. *Riv. Neurol.*, **1957**, *27*: 455-461.

PAMPIGLIONE, G. et MARTIN, F. Périodicité de quelques phénomènes cérébraux. Etude électroencéphalographique. *Arch. Suiss. Neurol. Psychiat.*, **1953**, *71*: 277-284.

PINELLI, P. L'elettroencefalografia nelle encefaliti. *Atti XII Congr. Soc. It. Neurol.*, Edit. Calia, Napoli, **1958**: 95-199.

RADERMECKER, J. Aspects électroencéphalographiques dans trois cas d'encéphalite subaiguë. *Acta Neurol. Psychiat. Belg.*, **1949**: 222-232.

RADERMECKER, J. Systématique et électroencéphalographie des encéphalites et encéphalopathies. *EEG Clin. Neurophysiol.*, Suppl. No 5, **1956**, 243 pp.

SANGUINETI, I. E GUARESCHI, A. Contributo allo studio elettroencefalografico delle encefaliti. *Arch. Psicol. Neurol. Psichiat.*, **1952**, *13*: 549-583.

SANGUINETI, I. E GUARESCHI, A. Sulla specificità dei ritmi elettrici cerebrali nella leucoencefalite sclerosante subacuta (L.E.S.S.). *Atti XII° Congr. Soc. It. Neurol.*, Edit. Calia, Napoli, **1958**: 429.

STRICH, S. J. Altered states of consciousness due to white matter degeneration I. Cong. Inter. Scien. Neurol. Bruxelles, *Acta Med. Belg.* **1957**, *2*: 111-114.

TERZIAN, H. Su un particolare quadro EEG delle encefaliti nell'infanzia. Considerazioni sui fenomeni periodici in elettroencefalografia. *Riv. Neurol.*, **1955**, *25*: 568-578.

VIZIOLI, R. E MACCAGNANI, F. I fenomeni periodici in elettroencefalografia clinica. *Riv. Neurobiol.*, **1955**, *1*: 257-262.

Reference : ZAPPOLI, R. Transient electroencephalographic pattern characteristic of sub-acute leuco-encephalitis in a case of acute head injury. *EEG Clin. Neurophysiol.*, **1959**, *11*: 571-575.

PRINTED IN GERMANY

THE PREVENTION OF THE TRANSMISSION OF VIRAL HEPATITIS BY NEEDLE ELECTRODES

HAROLD O. CONN, M.D.[1] and RUTH E. NEIL [2]
Medical Service and Section of Neurology, Veterans Administration Hospital, West Haven, Conn., and the Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn.

(Received for publication: July 21, 1958)

The major potential hazard of electroencephalography and electromyography is the transmission of viral hepatitis. The increasing use of needle electrodes, which replace disc electrodes, is responsible for this danger. Needle electrodes, which can be introduced into the subcutaneous tissues almost painlessly, are faster, simpler, and establish better electrical contact than do the external disc electrodes. Unfortunately, needle electrodes do not withstand repeated sterilization by boiling or autoclaving. Although the practices of "cold sterilization" by immersion in germicidal solutions or exposure to ultra-violet light are used in many electroencephalographic laboratories, these techniques do not destroy the virus of hepatitis (Neefe 1946).

Although no case of viral hepatitis has yet been reported to have been transmitted in this manner, it is almost certain that this mode of transmission occurs. Hepatitis previously has been shown to have been transmitted by contaminated needles, syringes, lancets, dental tools and tattoo needles (Capps *et al.* 1948; Smith 1950; Steigmann *et al.* 1950). The existence of healthy hepatitis carriers makes it almost impossible to avoid contamination of these needles (Stokes *et al.* 1954). The recent interest in the electroencephalographic abnormalities of liver disease presages increased risk of the transmission of viral hepatitis (Foley *et al.* 1950; Parsons-Smith *et al.* 1957).

The convenience and efficiency of needle electrodes would be more than offset by the inadvertent transmission of viral hepatitis, or by the need to discard these electrodes after each usage. The purpose of this communication is to focus attention on this danger, and to describe a simple, inexpensive means of sterilizing these electrodes.

The apparatus consists of a wooden electrode holder which allows immersion of the needle in boiling water without exposure of the heat labile portions of the needle electrode. It is made from a ¾" block of buoyant wood in which holes have been drilled according to the specifications in figure 1, or to support similar electrodes of any size. The electrodes are inserted in these holes so that the needle portion projects through the bottom, figure 2. The block with

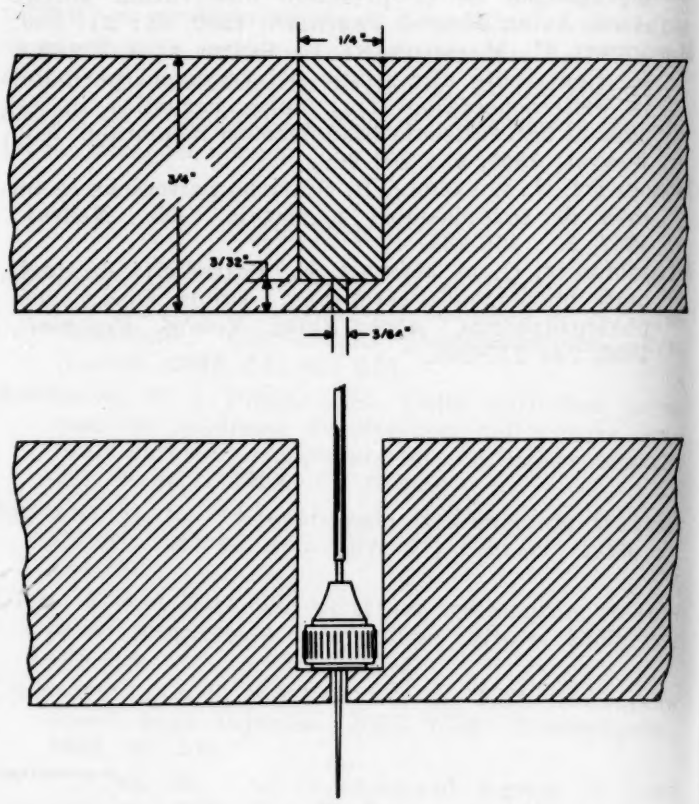


Fig. 1
Cross section of wooden electrode holder showing (above) specifications, and (below) needle electrode in place.

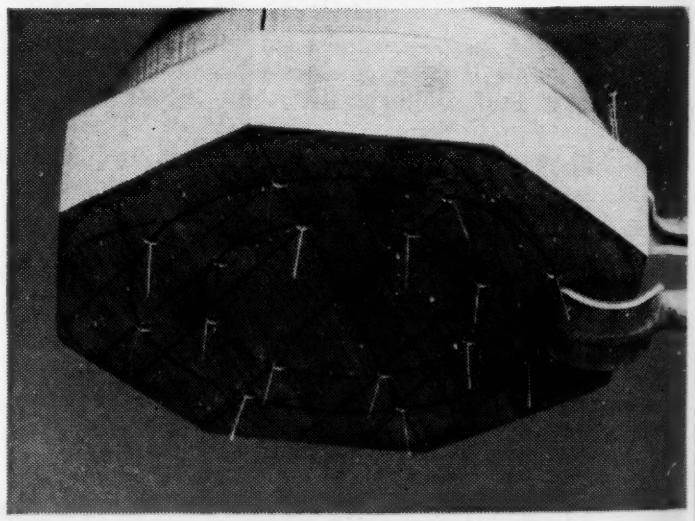


Fig. 2
Enlargment showing needle portion of electrodes projecting through electrode holder.

1 Clinical Investigator, Veterans Administration Hospital, West Haven, Conn., and Assistant Professor of Internal Medicine, Yale University School of Medicine, New Haven, Conn.
2 Electroencephalograph Technician, Veterans Administration Hospital, West Haven, Conn.

needles in place is floated in a water bath and boiled for 30 min. (fig. 3). The full length of the needle and its metal base are in contact with boiling water. As the water level recedes, the floating block keeps the needles entirely immersed. After sterilization the needles may be stored in sterile wrappings or a bactericidal solution until re-used. We have repeatedly sterilized needle electrodes over a period of six months without damage to them. This apparatus can be made in a few minutes in any simple carpentry shop at almost no cost.

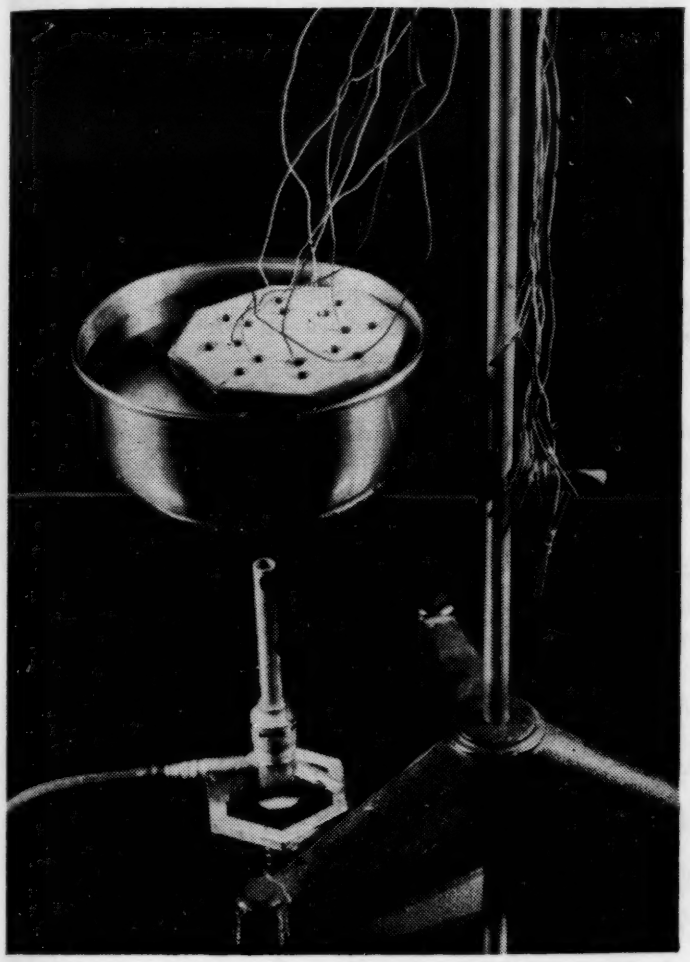


Fig. 3
The apparatus as it appears at the conclusion of sterilization.

Although the method described herein is a simple inexpensive means of sterilizing needle electrodes, the manufacture of electrodes which can be autoclaved would be a completely satisfactory solution to the problem.

The authors wish to thank Doctors Gilbert H. Glaser and Lewis L. Levy for their helpful suggestions.

REFERENCES

CAPPS, R. B., SBOROV, V. and SCHEIFFLEY, C. H. Syringe-transmitted epidemic of infectious hepatitis, with observations regarding incidence and nature of infectious donors. *J.A.M.A.*, **1948**, *136*: 819-824.

FOLEY, J. M., WATSON, C. W. and ADAMS, R. D. Significance of electroencephalographic changes in hepatic coma. *Trans. Amer. Neurol. Ass.*, **1950**, *75*: 161-165.

NEEFE, J. R. Recent advances in knowledge of "virus hepatitis". *M. Clin. North America*, **1946**, *30*: 1407-1443.

PARSONS-SMITH, B. G., SUMMERSKILL, W. H., DAWSON, A. M. and SHERLOCK, S. Electroencephalogram in liver disease. *Lancet*, **1957**, *2*: 867-71.

SMITH, B. F. Occurrence of hepatitis in recently tattooed service personnel. *J.A.M.A.*, **1950**, *144*: 1074-76.

STEIGMANN, F., HYMAN, S. and GOLDBLOOM, R. Infectious hepatitis homologous serum type in drug addicts. *Gastroenterology*, **1950**, *15*: 642-646.

STOKES, J., JR. and others. The Carrier state in viral hepatitis. *J.A.M.A.*, **1954**, *154*: 642-646.

Reference: CONN, H. O. and NEIL, R. E. The prevention of the transmission of viral hepatitis by needle electrodes. *EEG Clin. Neurophysiol.*, **1959**, *11*: 576-577.

PRINTED IN CANADA

LIMITES ET ÉVOLUTION ÉLECTRIQUE DE L'HYPSARYTHMIA [1]

D. SAMSON-DOLFUS, M.D.
Rouen, France

(Received for publication: September 19, 1958)

Ce travail repose sur 35 tracés enregistrés chez 15 enfants âgés de moins de trois ans, avec des altérations très importantes de l'électroencéphalogramme.

Ces altérations sont caractérisées par: l'absence complète du rythme de base normal correspondant à l'âge; l'existence de pointes et d'ondes lentes, et d'ondes lentes de très haut voltage, survenant à l'état de veille, dans la plus grande anarchie. La tendance vers l'aplatissement périodique du tracé de sommeil.

Parmi ces 15 enfants, deux groupes sont distingués d'emblée:

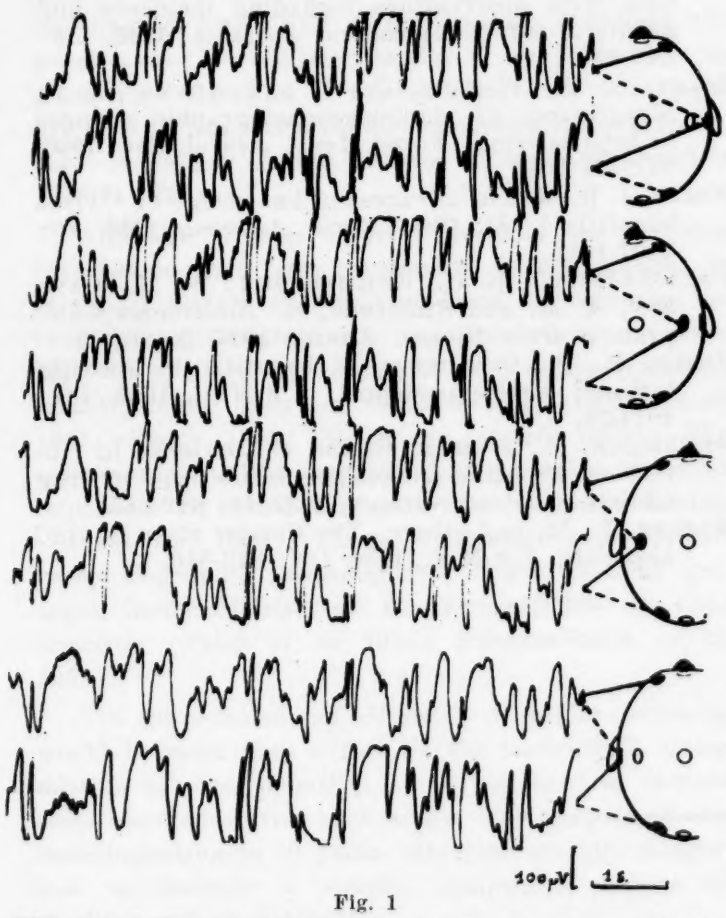


Fig. 1
LES. 2 ans. Tracé montrant l'aspect typique de l'hypsarythmia chez l'enfant éveillée ou discrètement somnolente.

Groupe I. Tracés d'hypsarythmia typique; 7 enfants.

Les altérations du tracé de veille sont diffuses et l'anarchie se retrouve aussi bien dans la topographie que dans la succession des images (fig. 1). Dans le sommeil profond, les altérations ont tendance à se grouper en bouffées périodiques (fig. 2). L'anarchie du tracé de veille persiste dans le sommeil.

Groupe II. A la différence de l'hypsarythmia typique, on retrouve une ébauche d'organisation; 8 enfants.

Organisation topographique: les altérations prédominent en avant, en arrière ou sur un hémisphère (fig. 3).

Organisation pseudorythmique, une grande pointe diffuse paraît survenir de façon rythmique sur le fond pathologique de l'EEG. Cet aspect est particulièrement net dans le sommeil (fig. 4 et 5).

Ces deux groupes ont-ils la même signification? Etablis comme nous venons de le voir sur des caractères électriques un peu différents, ils ne présentent aucune différence du point de vue clinique:

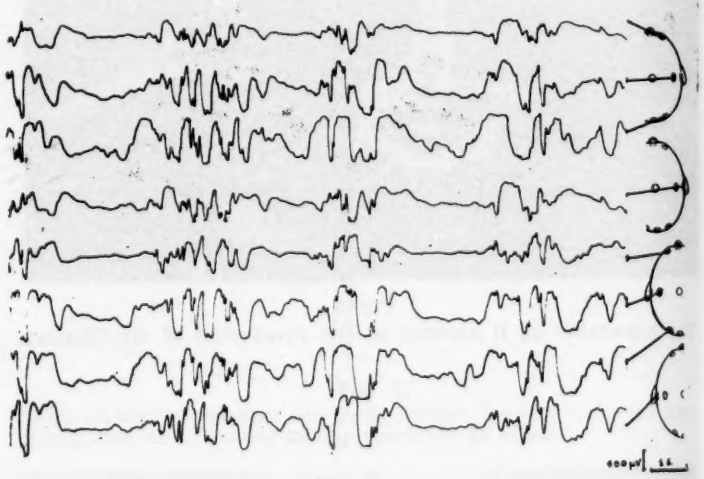


Fig. 2
L. 4 mois. Aspect périodique du tracé de sommeil profond d'un enfant présentant une hypsarythmia; les figures amples sont séparées par des intervalles de « silence » électrique. (Montage référentiel.)

le retard psychomoteur existe toujours et il est proportionnellement d'autant plus important que la maladie a commencé plus jeune, ou que l'on se trouve plus près de l'épisode initial (fig. 6 A et B);

l'histoire clinique comporte l'existence de manifestations critiques plus ou moins typiques, de mâchonnements, ou de troubles paroxystiques du tonus (ceux-ci ne sont pas toujours des spasmes en flexion, mais peuvent être des spasmes en extension ou de brèves chutes de la tête);

l'étiologie est très polymorphe dans le premier et le second groupe, mais ces syndromes électriques sem-

1 Résumé d'un exposé fait le 8 février 1958 à l'Hôpital de la Pitié, dans le cadre des séminaires sur l'EEG de l'enfance organisés par H. Fischgold et C. Dreyfus-Brisac.

blent être plus fréquents après une maladie infectieuse ou inflammatoire qu'après un traumatisme obstétrical (fig. 8) ;

l'évolution clinique semble aussi grave dans les deux groupes; l'enfant peut finir par avoir un développement physique et moteur, normal, mais n'a aucune évolution intellectuelle (fig. 6), (l'un de ces enfants les plus atteints marche parfaitement, monte

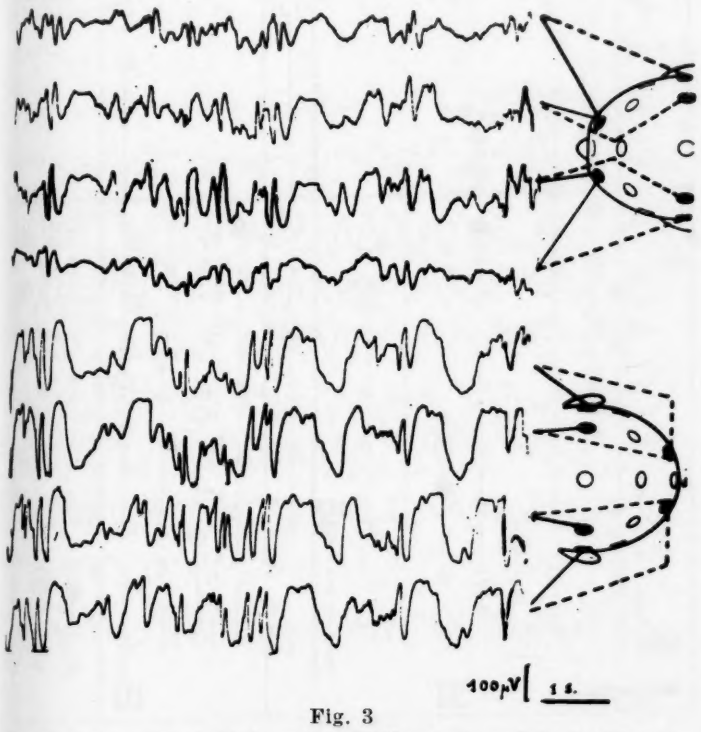


Fig. 3

R. 26 mois. Tracé légèrement différent de celui de l'hypsarythmia. Ici, les altérations sont plus amples en arrière; 2 mois plus tard, tracé typique d'hypsarythmia, qui a disparu ultérieurement.

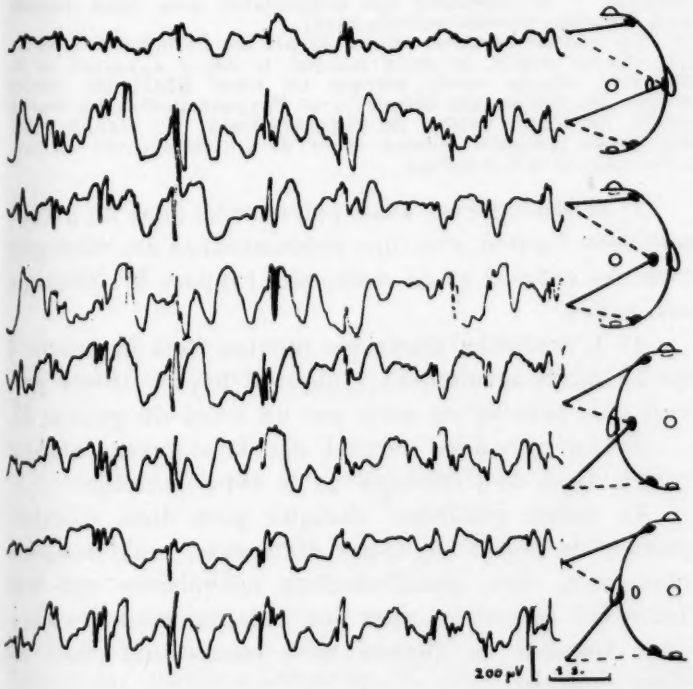


Fig. 4

R. 26 mois. Tracé de sommeil montrant l'apparition pseudo-rythmique d'une pointe diffuse, survenant sur un fond très pathologique.

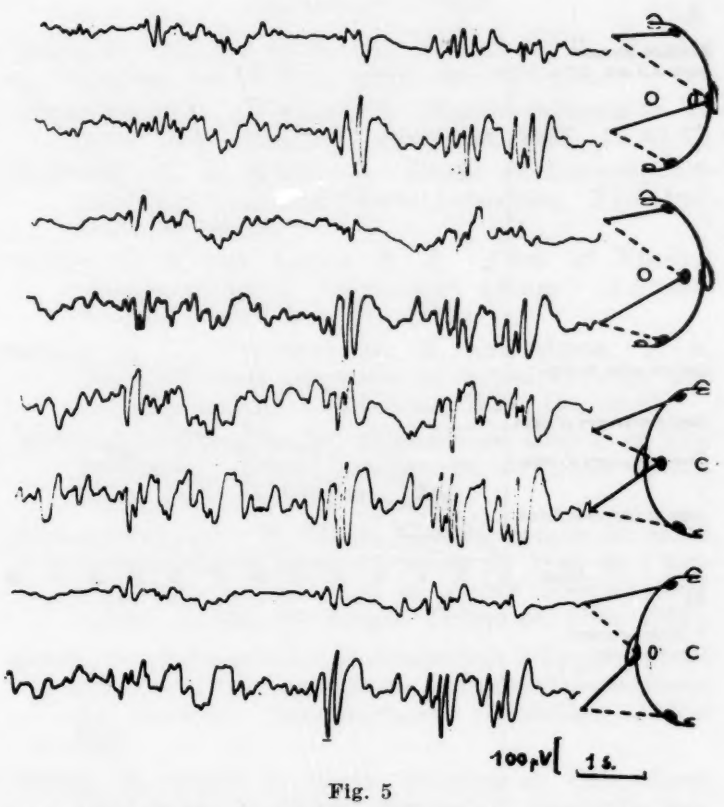


Fig. 5

AU. 17 mois. Tracé de sommeil d'un enfant n'ayant jamais présenté une hypsarythmia typique, mais qui, à l'âge de 3 ans, n'a aucun contact avec son entourage, ne parle pas et marche seulement depuis deux mois.

les escaliers, mais n'obéit à aucun ordre, ne joue à rien qu'à taper sur une balle ou à déchirer du papier).

Du point de vue électrique, nous voyons que les tracés du groupe II peuvent précéder l'apparition d'un tracé typique du groupe I ou groupe d'hypsarythmia. De même, qu'un tracé II peut suivre un tracé I (fig. 7 et 8).

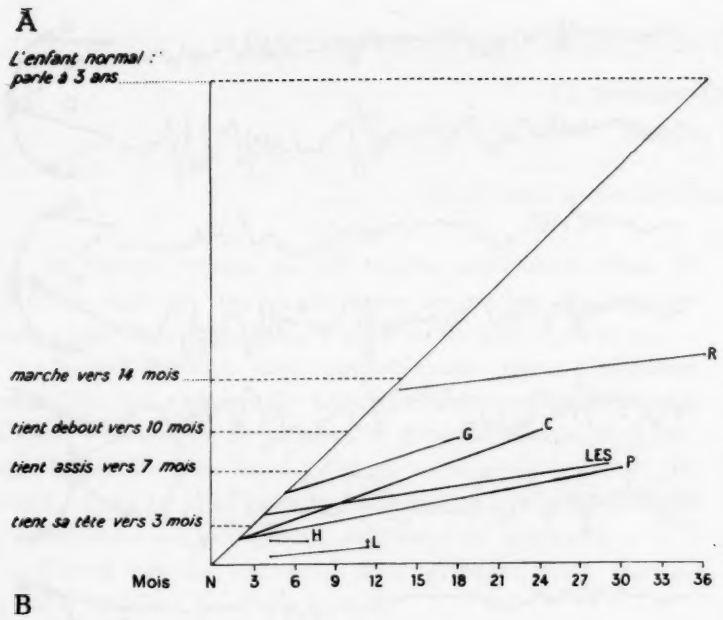
En conclusion, nous avons comparé des tracés typiques d'hypsarythmia avec des tracés très voisins, mais qui ne peuvent y être rattachés que partiellement. Les uns et les autres peuvent se voir chez le même enfant.

CONCLUSIONS

Le même syndrome clinique comportant une détérioration psychique particulièrement sévère, associée à des manifestations convulsives, survenant au cours des deux premières années de la vie peut s'accompagner de tracés de types différents.

Des manifestations convulsives ont toujours été rencontrées chez ces enfants, mais les typiques spasmes en flexion sont inconstants aussi bien dans le groupe de l'hypsarythmia que dans le groupe annexe.

Les formes voisines de l'hypsarythmia ont la même signification pronostique que l'hypsarythmia elle-même: ce sont des tracés qui ont tous un caractère de très haute gravité.



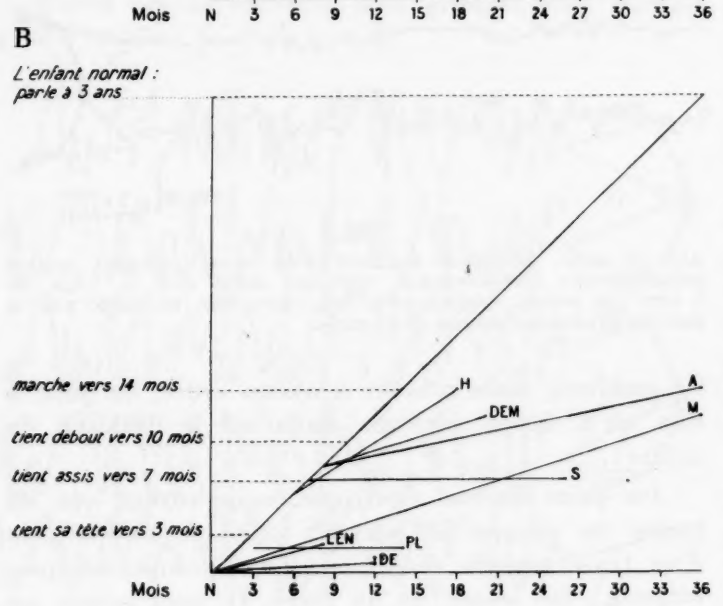


Fig. 6 A

Tableau montrant l'évolution clinique schématique de 7 enfants ayant présenté au moins une fois un tracé typique d'hypsarythmia. En ordonnée, les grands repères de l'évolution psychomotrice de l'enfant de 0 à 36 mois (tient sa tête, tient assis, marche, parle etc.) ; en abcisse, l'âge. La diagonale montre le développement schématique d'un enfant normal ; les 7 autres courbes montrent le développement des enfants malades : plus la maladie commence tôt, plus le développement de l'enfant est retardé, plus la droite a tendance à se rapprocher de l'horizontale.

Fig. 6 B

Même type de tableau que le précédent ; celui-ci concerne les 8 enfants ayant eu un tracé voisin, mais non typique d'hypsarythmia.

RÉSUMÉ

Nous avons étudié 15 enfants âgés de moins de 3 ans, ayant eu des altérations très importantes de leur EEG (35 tracés).

1) Deux groupes ont été distingués. Dans le premier groupe (7 cas), les enfants ont eu chacun au moins une fois un tracé typique d'hypsarythmia. L'autre groupe (8 cas) montrait quelques différences avec l'hypsarythmia typique. Ces différences portent soit sur l'organisation topographique du tracé, soit sur la succession des figures pathologiques (veille, somnolence, sommeil).

2) Cliniquement, l'aspect est le même dans les 2 groupes. Une grande détérioration mentale est rapidement associée ou suit des manifestations convulsives de type variable.

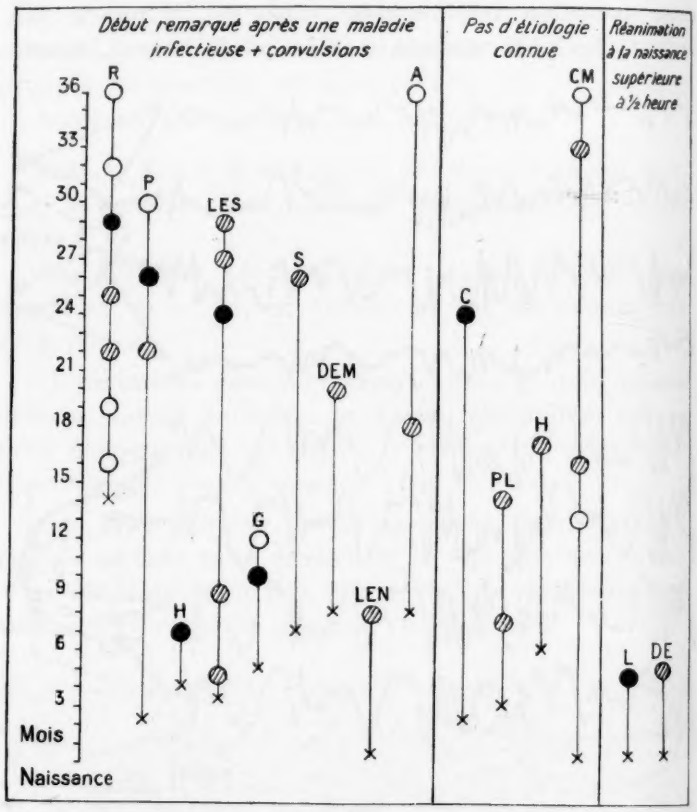


Fig. 7

Tableau * montrant :
1) que sur 15 cas, la maladie s'est développée 9 fois après une maladie infectieuse ou inflammatoire, associée à des convulsions ; 4 fois, l'étiologie n'a pu être précisée ; 2 fois, la réanimation à la naissance est indiscutable (ces deux enfants sont les seuls décédés actuellement).
2) l'âge (donné en mois) est représenté sur l'échelle de gauche ; sur chaque droite, la croix marque le début apparent de la maladie ; chaque cercle marque un tracé EEG : les cercles blancs, les tracés sans rapport avec l'hypsarythmia ; les cercles rayés, les tracés voisins de l'hypsarythmia ; les cercles noirs, les tracés typiques. Divers types de tracés peuvent se succéder chez le même enfant.

3) L'étiologie est aussi polymorphe dans un groupe que dans l'autre, avec une prédominance des étiologies acquises entre 2 et 14 mois, par rapport à l'étiologie néo-natale.

4) L'évolution électrique montre dans le groupe I qu'un tracé absolument typique d'hypsarythmia pouvait être précédé ou suivi par un tracé du groupe II.

5) Le pronostic mental est très grave, quelque soit le type de l'étiologie ou le type électrique.

Le même syndrôme clinique peut donc s'accompagner de tracés de types différents, mais toujours anormaux. Des manifestations convulsives ont toujours été retrouvées chez ces enfants, mais les typiques spasmes en flexion sont inconstants dans les deux groupes.

*** Les parties de ce tableau montrant l'évolution électrique des cas enregistrés plusieurs fois ont été réalisées avec la collaboration de R. Dailly, C. H. de Menibus, F. Nicolle.**

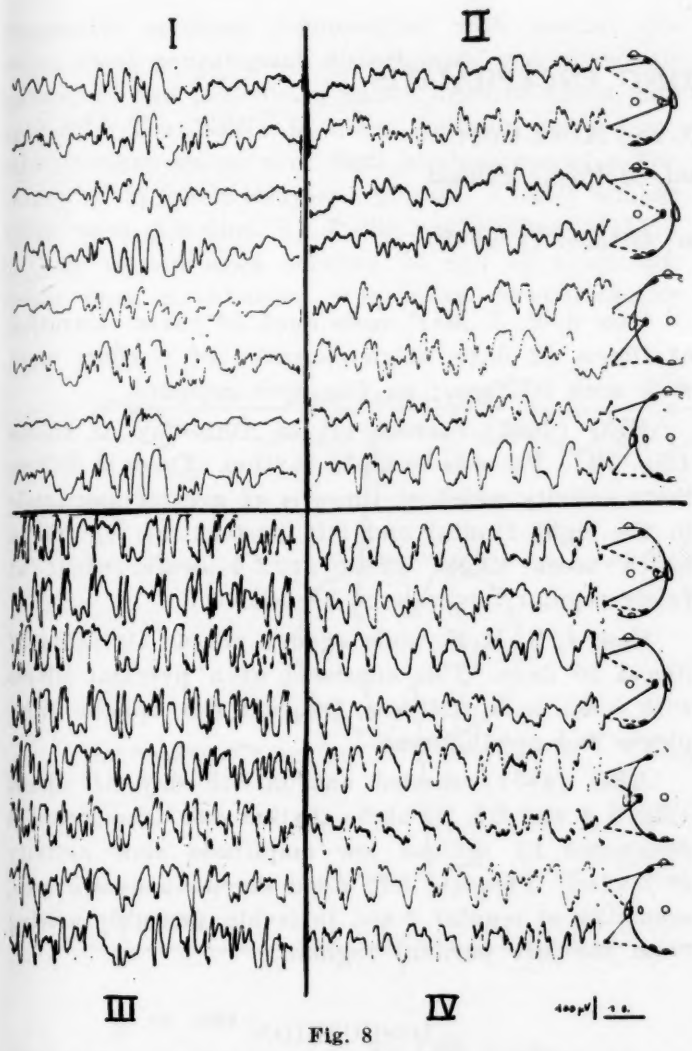


Fig. 8

Enfant LES. I. 4 mois — II. 9 mois — III. 2 ans — IV. — 2 ans 2 mois. Chez cette enfant, seul le tracé III est typique d'hypsarythmia ; les 3 autres tracés montrent d'importantes altérations non typiques.

BIBLIOGRAPHIE

CHAO, D., TAYLOR, F. M. and DRUCKMAN, R. Massive spasms. *J. Pediat.*, **1957**, *50*: 670-678.

DRUCKMAN, R. and CHAO, D. Massive spasms in infancy and childhood. *Epilepsia*, **1955**, *4*: 61-72.

GASTAUT, H. et ROGER, A. Etude électroencéphalographique des convulsions infantiles. *Pédiatrie*, **1953**, *8*: 608-613.

GIBBS, F. A. and GIBBS, E. L. *Atlas of Electroencephalography.* Cambridge (Mass.) Addison-Weseley press. Vol. 11. **1952**.

GIBBS, E. L., FLEMING, M. H. and GIBBS, F. A. Diagnosis and prognosis of hypsarhythmia and infantile spasms. *Pediatrics*, **1954**, *13*: 66-73.

REBUFAT-DESCHAMPS, M. Spasmes en flexion et hypsarythmia. Etude critique de 30 observations. Thèse, Paris, Foulon éd., **1958**.

SAMSON-DOLLFUS, D. Etude électro-clinique de crises enregistrées au cours de tracés du type de l'hypsarythmia. (à paraître in *Revue Neurologique*. Société d'EEG de langue française, Déc. **1957**).

SOREL, L. Tableau d'un traitement de l'hypsarythmia par l'A.C.T.H. exposé au Congrès International des Sciences Neurologiques. Bruxelles, Juillet **1957**.

SOREL, L., GIBBS et GIBBS, STAMPS et Coll., LOW, KELLAWAY, P., POSER, BOSMA, J. Scientific conference on A.C.T.H. Treatment of Infantile spasms and hypsarhythmia. *Med. Sci.*, **1958**, *8*: 457-462.

THIEBAUT, F., SACREZ, R., ROHMER, F. et ISCH-TREUSSARD, C. Corrélations électro-cliniques dans 25 cas d'hypsarythmia de Gibbs. *Rev. Neurol.*, **1955**, *93*, 455-460.

THIEFFRY et AICARDI, J. Les spasmes en flexion du nourrisson; 36 observations, étude clinique. *Sem. Hôp.* **1958**, *19*: 1168-1178.

Reference: SAMSON-DOLLFUS, D. Limites et évolution électriques de l'hypsarythmia. *EEG Clin. Neurophysiol.*, **1959**, *11*: 579-583.

PRINTED IN CANADA

THE EEG IN NECROTIZING ENCEPHALITIS

J. H. D. Millar, M.D. and Alice Coey
Royal Victoria Hospital, Belfast, Ireland

(Received for publication: October 17, 1958)

This communication is to amplify the information concerning the EEG given in a previous paper by Crawford and Robinson (1957). They reported the clinical and pathological findings in 5 cases of necrotizing encephalitis. In 3 cases EEGs had been carried out but no records were published. When we reviewed the EEGs it was seen that they had one feature in common; that was repetitive waves occuring regularly at 2-4 sec. intervals. As this is a rare pathological condition and the EEG abnormality unusual we considered it reasonable to publish these records. The full clinical and pathological details are available in the previous paper (Crawford and Robinson 1957) and only brief summaries of the clinical histories of the three patients who had EEGs carried out and a general statement about the pathological picture need be given.

At postmortem the cerebral cortex was necrotic and soft with evidence of increased intracranial pressure due to swelling. Histologically the affected areas of cortex showed loss of all nerve cells and destruction of myelin sheaths with replacement by large numbers of swollen astroglia and microglial cells. Varying numbers of plasma cells and lymphocytes were also present and the overlying meninges were similarly infiltrated. Vascular damage was relatively slight and not sufficient to have caused the necrosis. Other parts of the brain only rarely showed patches of frank necrosis but there was widespread perivascular cuffing. The cerebellum and spinal cord showed only slight changes. Demyelination was not a feature of these cases and was present only in the necrotic areas. No intranuclear inclusion bodies were found.

CASE HISTORIES

Case 1, K. M. female aged 30 years. Duration of illness 22 days. Sudden onset of coma, pyrexia and neck stiffness following a fit. Six days later a second fit occurred, and further frequent major fits affecting at times more one side of the body and at times the other side, preceded her death.

EEG (1537) carried out 9th day of illness (fig. 1A). There is no alpha rhythm. The record is generally abnormal showing diffuse slow activity. Sharp waves are seen in the right frontal region where they are sometimes focal and tend to occur at regular 2 sec. intervals.

Case 3, P. J. McF. male aged 59 years. Duration of illness 22 days which consisted of a coma state with neck stiffness; no fits were reported.

EEG (2880) carried out on 10th day of illness (fig. 1B). There is no alpha rhythm. There is diffuse theta activity which at times is of greater amplitude in the right frontal and left postcentral regions in which areas single waves at 2-4 c/sec. occur at fairly regular intervals of 3-4 sec.

Case 4, S. McK. male aged 2 years. Duration of illness 50 days. This consisted of a pyrexial illness with coma, neck stiffness, frequent fits, spastic paraplegia and opisthotonus.

EEG (4851) carried out on 4th day of illness (fig. 2 A and B). No alpha rhythm seen. The record is dominated by diffuse low amplitude slow activity at 1 c/sec. Frequent left sided sharp waves are seen, occurring at regular 2 sec. intervals, probably arising from the left parietal region.

DISCUSSION

Greenfield (1950) reported two similar cases but no EEG was mentioned. Van Bogaert, Cordier and Hennaux (1955) also published one case and no EEG was carried out. However, Van Bogaert, Radermecker and Devos (1955) reported a case of acute necrotizing encephalitis in whom two EEGs were carried out. The records were abnormal and in one there were sharp waves, but from the specimens of record shown there is no evidence of repetitive waves at regular intervals. We should emphasise that this striking feature is not always bilateral and generalised but is usually limited to electrodes covering limited areas of the scalp. The possibility that the abnormality might be due to artefact was considered but rejected as it seemed most unlikely that this artefact should be confined to the three cases of necrotizing encephalitis out of a total to date of 16,000 EEGs carried out in this department.

The EEG of subacute inclusion encephalitis and subacute sclerosing leucoencephalitis (Radermecker 1949; Cobb and Hill 1950; Foley and Williams 1953) is different from the records described here, in which the periodicity is different, the intervals between the discharges are shorter and the complexes of shorter duration. Jones and Nevin (1954) describe a rapidly

progressive cerebral degeneration with mental disorder, focal neurological disturbances and myoclonic epilepsy in two patients, a women aged 66 and a man aged 62. The EEGs in these patients showed recurrent sharp waves over both hemispheres at a frequency of approximately one per sec. Closely similar EEGs were described by Pallis and Spillane (1957) in three women aged between 45 and 55 years suffering from a subacute progressive encephalopathy of the frequency of the repetitive discharges. In addition the clinical picture is different; no myoclonus was observed and the course of the disease was more rapid in the patients suffering from necrotizing encephalitis.

The authors quoted above stress the importance of subcortical structures in the production of the repetitive waveforms. The cases here described emphasise the importance of the cortex in as much as the

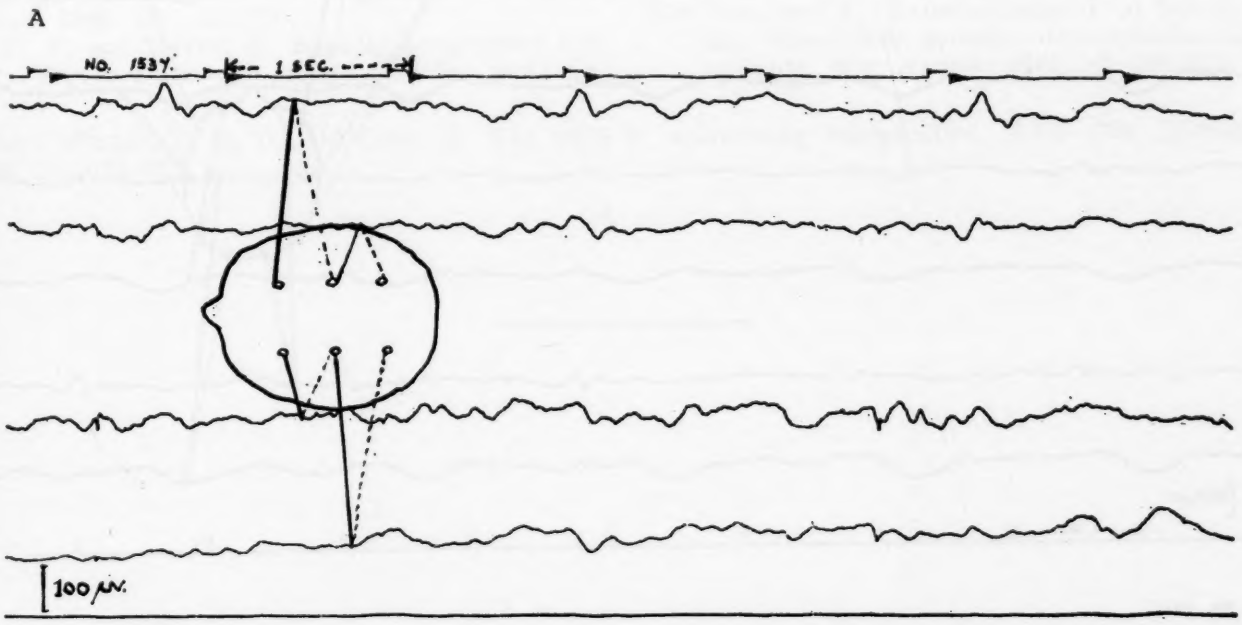


Fig. 1

with mutism, hypokinesia, rigidity and myoclonus. The EEG in this condition showed long runs of regular high voltage polyphasic complexes occurring at a rate of 2 per sec.

The EEGs described in this communication fall between the pattern associated with the subacute inclusion encephalitis group and patterns for the encephalopathies described by Jones and Nevin (1954) and Pallis and Spillane (1957) from the point of view cortex sustained the brunt of the disease process, and the EEG discharges appeared to be localised to definite cortical areas and were only rarely bilaterally synchronous or generalised.

SUMMARY

The EEGs of three cases of necrotizing encephalitis are reported. The records showed repetitive waves occurring regularly at 2-4 sec. intervals.

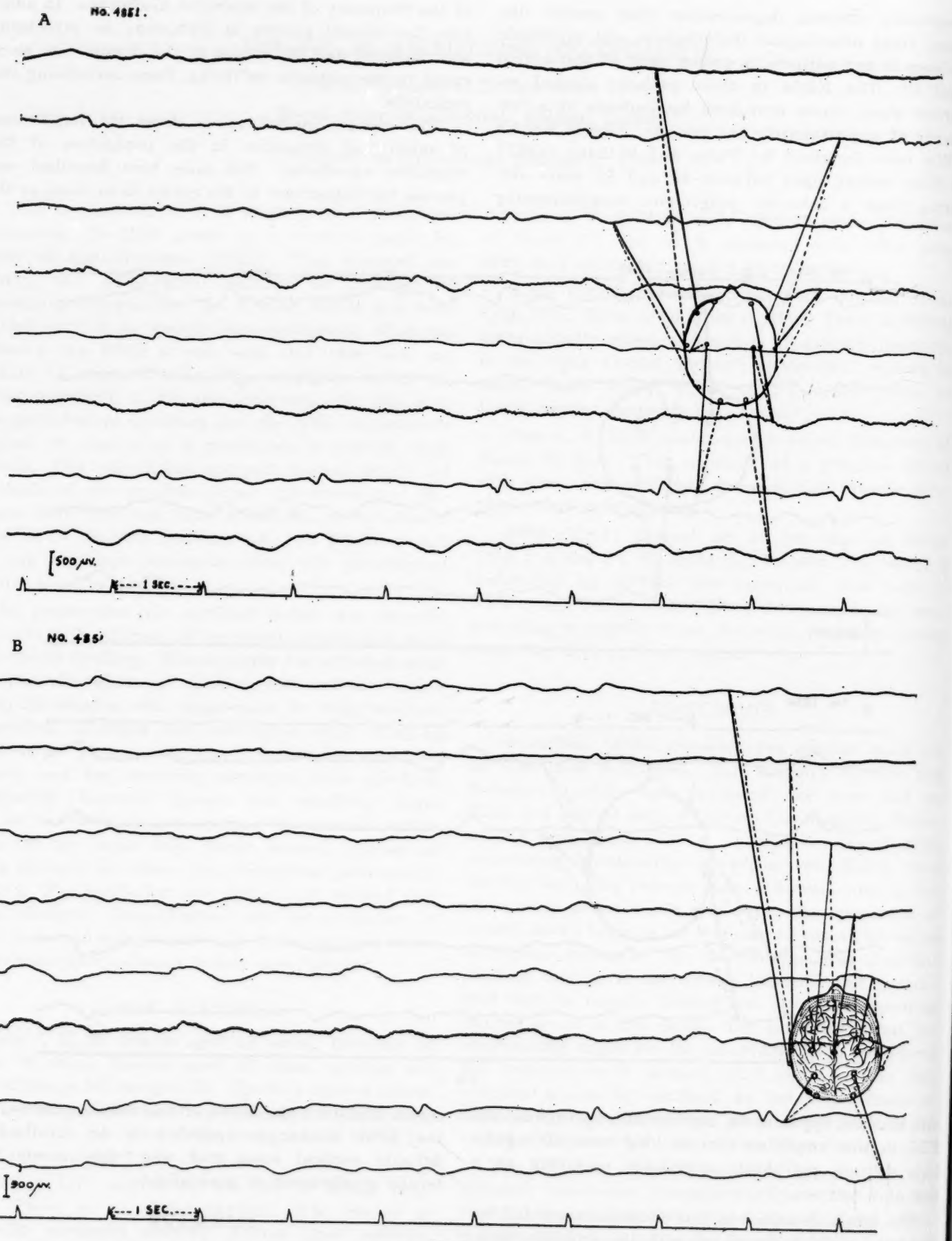


Fig. 2

REFERENCES

COBB, W. and HILL, D. Electroencephalogram in subacute progressive encephalitis. *Brain*, **1950**, *73*: 392-404.

CRAWFORD, A. R. and ROBINSON, L. J. Necrotizing encephalitis. *Brain*, **1957**, *80*: 209-221.

FOLEY, J. and WILLIAMS, D. Inclusion encephalitis and its relation to subacute sclerosing leucoencephalitis. *Quart. J. Med.*, **1953**, *22*: 157-194.

GREENFIELD, J. G. Encephalitis and encephalomyelitis in England and Wales during the last decade. *Brain*, **1950**, *73*: 141-166.

JONES, D. P. and NEVIN, S. Rapidly progressive cerebral degeneration with mental disorder, focal disturbances and myoclonic epilepsy. *J. Neurol. Neurosurg. Psychiat.*, **1954**, *17*: 148-159.

PALLIS, C. A. and SPILLANE, J. D. A subacute progressive encephalopathy with mutism, hypokinesia, rigidity and myoclonus. *Quart. J. Med.*, **1957**, *26*: 349-374.

RADERMECKER, J. Aspects électroencéphalographiques dans trois cas d'encéphalite subaiguë. *Acta Neurol. Psychiat. Belgica*, **1949**, *49*: 222-232.

VAN BOGAERT, L., CORDIER, J. et HANNEUX, J. Sur une encéphalite nécrotissante aiguë mortelle. *Bull. Acad. Roy. Méd.* Belg., **1955**, *20*: 145-156.

VAN BOGAERT, L., RADERMECKER, J. et DEVOS, J. Sur une observation mortelle d'encéphalite aiguë nécrosante. *Rev. Neurol.*, **1955**, *92*: 329-356.

Reference: MILLAR, J. H. D. and COEY, A. The EEG in necrotizing encephalitis. *EEG Clin. Neurophysiol.*, **1959**, *11*: 582-585.

POSITION WANTED

Experienced male EEG Technician desires changes from present position. Reply to EEG JOURNAL, 3801 University Street, Montreal, Canada.

PRINTED IN CANADA

TECHNICAL NOTES

Edited by H. SHIPTON, A. M. BRIT, I.R.E. and F. BUCHTHAL, M.D.

A SIMPLE DEVICE FOR MINIMISING THE EFFECTS OF "BLOCKING" IN RESISTANCE-CAPACITY COUPLED AMPLIFIERS

E. K. WITTRICK
Neuro-Psychiatric Department, Musgrove Park Hospital, Taunton, Somerset, England

(Received for publication: July 20, 1958)

The large majority of EEG machines used in the British Isles, and many used elsewhere, employ resistance capacity coupled valve amplifiers. These are inherently subject to ''blocking''.

A simple device is described to eliminate delays experienced from ''blocking'' during routine recording from handling of electrodes, checking of electrode resistances, changes of connection pattern, etc.

It is arranged to act upon the amplifiers at the first R-C coupling and consists of a set of relays arranged to connect the control grids of the valves of the following stage to earth when the machine

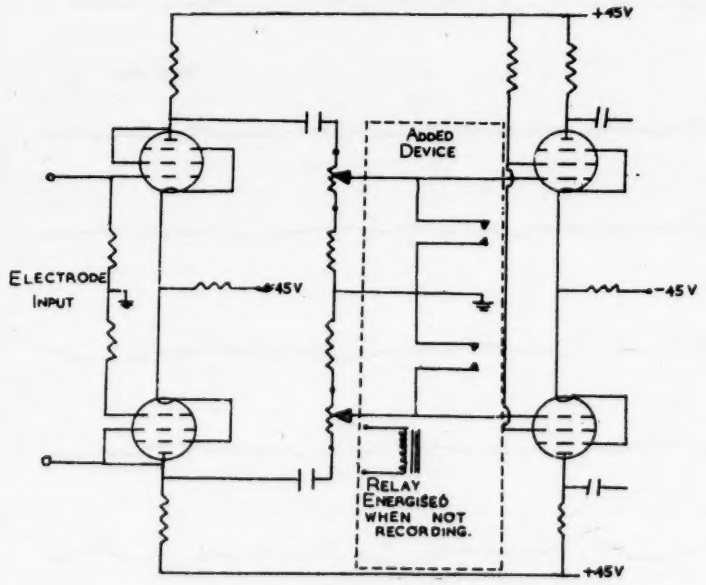


Fig. 1
Ediswan preamplifier showing anti-blocking relay arrangement.

is not actually recording (fig. 1). This produces equilibrium in this coupling (and with it the following ones) very quickly.

The method described above has been applied to an Ediswan Mark 2A machine, a type which shows severe ''blocking'' due to the long time constant of its first to second stage coupling and its use of two following couplings. The earth connections thus are made by standard Post Office type 3000 relays operated by a micro-switch and cam on the paper drive switch shaft. Four relays are employed, each serving two amplifiers. It is found desirable to delay the closure of the relays by about half a second by connecting a large capacitor across the relay coils (which are in series) to minimise inductive surges. The relays are energised when the paper drive is off, so that any failure in the relay chain does not prevent the machine working. The arrangement does not affect the frequency or phase response of the machine in any way.

In this installation, delays due to the causes mentioned are reduced to the order of 1 or 2 sec. It is also applicable to the elimination of ''blocking'' due to stimulus artifacts when cortical and other stimulation are employed, by the operation of the relay chain from the stimulation device. Where large changes, of the order of 1 V., in the D.C. input level are expected, some delay in accommodation of the electrode — first stage system is experienced as the time constant of the first stage anode resistors and coupling condensers becomes important, and it is necessary to delay the closure of the relays by 3 to 5 sec. in order to obtain a recording at the earliest possible point. This effect is less serious with pulses which return to the same D.C. base line, than with high amplitude D.C. changes.

SUMMARY

A simple device is described which can be fitted easily and cheaply to any R-C coupled electro-physiological amplifier. It reduces blocking delays during routine recordings to the order of 1 second and those due to stimulus artifacts to the order of 5 sec.

The author wishes to thank Dr. R. Sessions Hodge and Dr. J. W. Warboys for their interest and encouragement: Miss M. A. Stephens for technical assistance and the Taunton Hospital Management Committee and Mrs. Basil Ronald for making the work possible.

Reference: WITTRICK, E. K. A simple device for minimising the effects of ''blocking'' in resistance-capacity coupled amplifiers. *EEG Clin. Neurophysiol.*, **1959**, *11*: 586.

A METHOD FOR RECORDING AND REPRODUCING PROGRAMMED STIMULI: A BASIS FOR ACCURATELY EVALUATING THE CEREBRAL ELECTRICAL RESPONSE TO SENSORY STIMULATION [1]

JOHN HUNTER, M.D.,[2] C. WESLEY WATSON, M.D.[3] and JOHN DEGELMAN [4]
Department of Neurology, Neurosurgery and Psychiatry,
New England Center Hospital, Boston, Mass.

(Received for publication: July 27, 1958)

Intermittent photic stimulation with brief duration, high intensity flashes, in addition to providing a versatile physiological stimulus for the research worker, has been established as an important activating medium for routine use in the investigation of the epilepsies and for the routine screening of normal subjects in order to make manifest latent cerebral light sensitivity.

Despite the widespread adoption of relatively standard photic test equipment, the results from various electroencephalographic laboratories lack consistency. In small measure this variation is real, and is inherent to the test subject, but there is little doubt that a significant causal factor of variation in the same laboratory and in different laboratories is a lack of standardization in the application of the photic stimulus. A need for standard test stimuli is especially important when it is necessary to make accurate, comparative tests on the same subject — as for example, in the assessing of anticonvulsant therapy. It is equally necessary for studying the effect of environmental changes on cerebral light sensitivity in individuals or in groups.

To overcome this technical defect there has been developed an instrument, *Stimulus Program Unit* (fig. 1) and a method, *Stimulus Test Program*, whereby a simple or complex stimulus pattern of preselected frequency and intensity parameters, or alternatively, the particular parameters found to be most effective for a given test subject at the time of initial testing, may be recorded and preserved on ferromagnetic tape and subsequently used to retrigger the photic stimulus generator. The technique is devoid of errors in playback over and beyond the entire clinically useful frequency range (1 c/sec.-50 c/sec.) (fig. 2). The unit is simple in construction, and including the special unit, is composed of relatively inexpensive and easily obtainable components. Operation of the unit is easy and is aided by color coding of all controls.

The Stimulus Program Unit

Initial work on this project indicated that the major difficulties to be overcome, and those which led to an unfaithful reproduction of a program record-

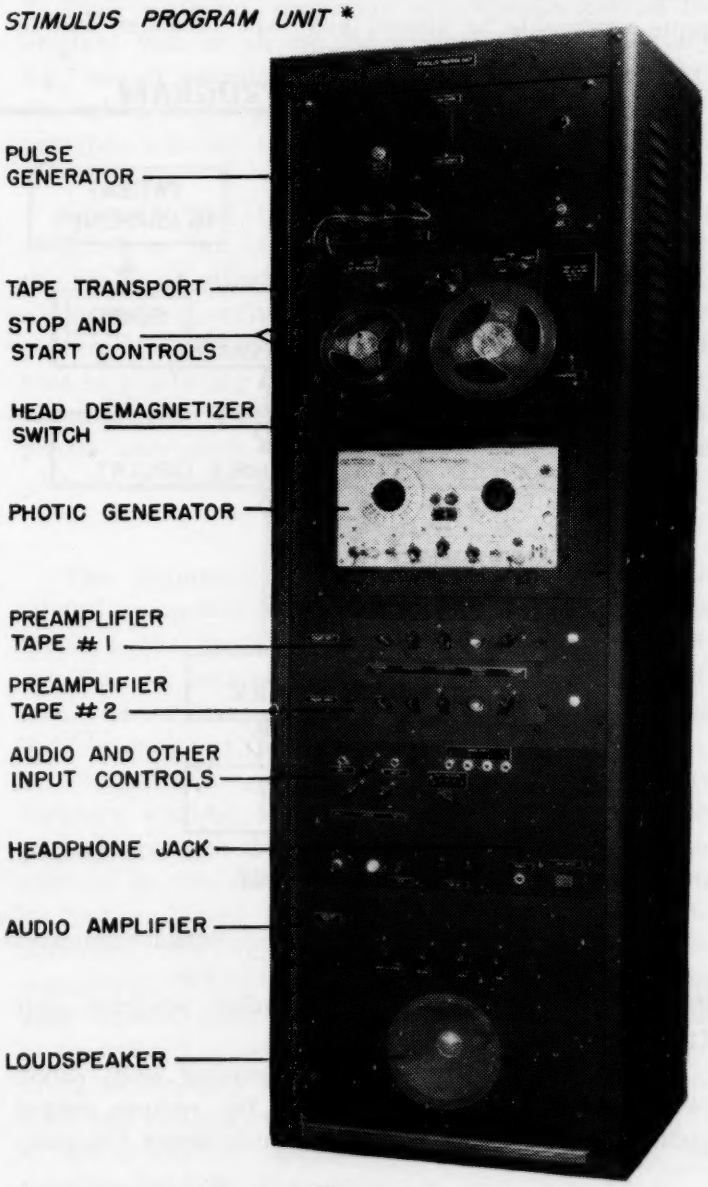


Fig. 1
To simplify operation, all **record** controls are labelled with a red dot and all **playback** controls with a green dot.

1 This investigation was supported by the Research and Development Division, Office of the Surgeon General, Department of the Army, under contract DA-49-007-MD-734-01.
2 Department of Surgery, Harvard Medical School and Department of Neurosurgery, Boston City Hospital, Boston, Mass.
3 Departments of Neurology, Neurosurgery and Psychiatry, New England Center Hospital.
4 Department of Biology, Boston University, Boston.

ed on tape were, firstly, distortion of the form of the recorded trigger signal by the tape itself, and, secondly, variations in the amplitude of the trigger signal. These latter resulted whenever a change of lamp intensity was effected, or they sometimes arose as a result of recording distortion. Although it was realized that the above difficulties could, in great measure, be overcome by using expensive high fidelity recording techniques or, alternatively, by a frequency modulation of the recording signal, a simpler method was sought and led to the development of a relatively inexpensive pulsing unit. This unit makes the technique applicable to almost any tape recorder and is the basic component of the stimulus program unit (fig. 1).

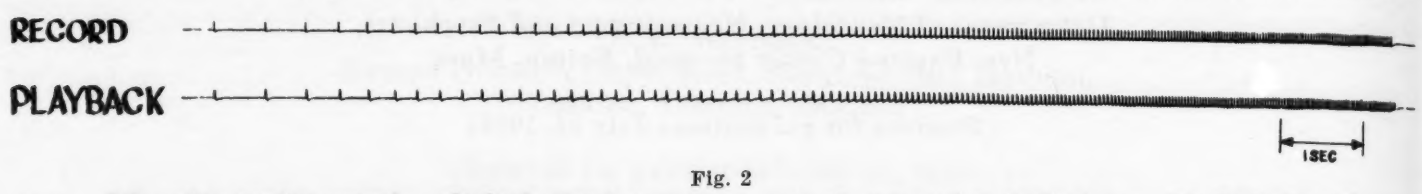


Fig. 2
Ink writer monitor **record - playback** signal comparison over the range 1-2 flashes/sec. - 36 flashes/sec.

Prior to development of the pulsing unit, direct recordings were made on tape of the various output pulses available from the Grass Instrument Company Photic Generator (Model P.S. 1). To effect playback these pulses were used as input signals for a Photic Generator Drive Unit [1] which reshaped the signal to a more optimal form for triggering the Grass Photic Generator (optimally a negative 50 V., 1 msec. pulse). This method did not prove to be satisfactory. Constant adjustment of the recording level was necessary with and without light intensity variations; constant adjustment of the photic drive unit potentiometer during playback was essential and cross modulation of the photic program channels added irregularities from the adjoining audio program on the second tape channel. Unsatisfactory, also, was a method which utilized the output of a photocell as a tape input signal. The chief disadvantage of this system was the variation of the trigger pulse as the result of a variation in light intensity. It did, however, serve to eliminate double pulses which, in the former method, were frequently encountered as output signals from the photic generator. By the use of the modified Schmitt trigger circuit it was possible to effectively

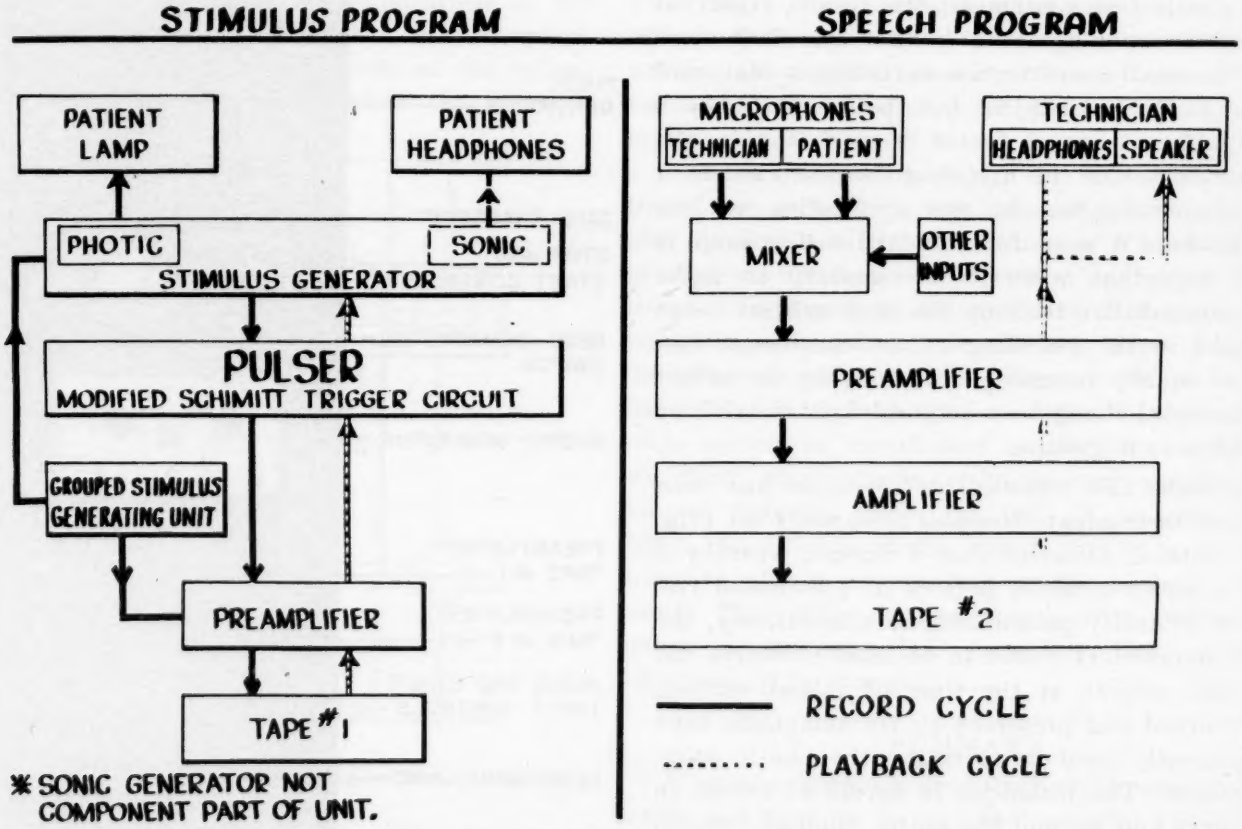


Fig. 3
Stimulus program unit component schema.

[1] This unit, originally described by Walter, Dovey and Shipton (1946) for synchronizing a photic generator with either analyzed or unfiltered brain rhythms, was made by the Grass Instrument Company.

overcome problems of double input pulses, cross modulation distortion, distortion of the wave form by the recording medium, the need for critical recording and playback adjustments and alteration in trigger pulses by variations in light intensity.

The stimulus program unit is designed for the programming of photic, sonic, or other intermittent stimuli, as well as for the recording of speech or music. The stimulus signal derived from a generator is the input to the pulsing unit. In the instance of the Grass Photic Generator (Model P.S. 1) this signal, obtained from the output labelled "Signal marker for EEG pen", is at intensity setting 1, a 5 V. saw-tooth pulse of positive sign and of duration 3 msec. Its amplitude varies with light intensity variation. In order to preserve an EEG signal marker, this output is paralleled. The arrangement of components is shown in the schema figure 3.

The pulsing unit is essentially a modified Schmitt (1938) (see also Chance 1949; Puckle 1955) trigger circuit whose output is a negative 50 V. square wave of 1 msec. duration irrespective of phase. This voltage range accommodates the entire range of the intensity control of the Grass Photic Generator. The output is independent of a change of input wave form providing that the wave form has a frequency component of not less than 1 c/sec. To effect playback, the recorded tape signal, now frequently biphasic due to distortion by the recording medium and with altered rise time, is applied to the input of the pulsing unit; the constant output now becomes the input trigger for the photic generator.

In instances where stimuli other than photic are required to be programmed, e.g., sonic "white noise" from a wide band noise generator, the sonic gating circuit timing pulse is substituted for the photic generator pulse (Hunter and Watson 1958). Playback, as before, is obtained by reshaping the tape signal and using it as the timing pulse for the gating circuit. Similar modifications might be made for other signal sources and effector units.

The second tape channel is available to record patient subjective sensations as well as significant observer remarks during flashing. It also serves to convey cues for a manual change of light intensity.

The stimulus program unit photic generator provides the standard frequency range of single flashes as well as coupled flashes separated by a variable delay. When it is desired to produce longer trains of regularly cycled interrupted stimuli, these may be effected by external gating circuit or by the use of two stimulators. Binding posts are available for these connections.

Intensity control, at the present time, is manually operated. An inaudible signal carried on the audio tape could be utilized to effect this control automatically. In order to extend the control of intensity beyond that provided by the standard position switch on the Grass Photic Generator, a series of capacitor decade boxes have been connected in parallel in place of the five standard capacitors connected to the intensity switch. For practical purposes a continuous control is thus obtained as well as an extended intensity range. (Intensity controls are not shown in fig. 1.)

The prototype stimulus program unit comprises the pulse generator; a Grass Instrument Company Photic Generator Model P.S. 1; two 30W record/playback Viking tape preamplifiers Model R.P. 61; a Viking # 75 tape deck; one Grommes # LJ5-10W amplifier; one Ampex head demagnetizer; one 6 inch loudspeaker. The various units are mounted on a mobile rack (fig. 1).

The photic generator is located at an optimum level for operation by a seated technician and may be used independently of the tape recorders.

Once recorded, programs are reproducible on the original unit or on similar equipment. If necessary, e.g., use at recruit or employment screening centers, the stimulus program unit could be reduced to a portable size by the use of standard miniaturizing techniques.

Stimulus test programs may be arbitrarily constructed, as far as it is possible to do so, to include the range of stimulus variation to be encountered in a particular environment. Alternatively, individual patterns may be constructed on the basis of effectiveness in producing an EEG change at the time of any examination. Test programs comprising combined photic and sonic stimuli may be readily produced with the stimulus program unit.

DISCUSSION

The important parameters of repetitive photic stimuli comprise: (1) flash duration; (2) flash intensity; (3) flash color; (4) flash frequency; (5) duration of dark period; (6) total average illumination. An additional factor of importance is ambient light intensity at the time of examination.

The stimulus program unit provides, or allows, accurate control and calibration of each of these parameters with the exception of flash duration. Variations in this latter parameter are presently being studied and will be reported on at a later time. Ambient room lighting is calibrated and controlled separately. While the value of stimulus test programs must not be overemphasized, they must nevertheless be recognized as being prerequisite to any study undertaken to evaluate variations observed in light evoked EEG and clinical responses.

An accurately reproducible stimulus test program satisfies the following needs:

1. A standardized source of comprehensive and accurately repeatable stimuli for the detection of ab-

normal light stimulus sensitivity in individuals or in group testing, e.g., helicopter pilot recruits; public transport vehicle operator applicants; family groups where genetically determined cerebral light sensitivity (Davidson and Watson 1956) is suspected.

2. A prerequisite to the quantitative measurement of degree of cerebral light sensitivity in the human subject (or in the animal) made light sensitive, as by Metrazol.

3. A prerequisite for accurate assay of therapeutic effectiveness in light sensitive human subjects.

4. A means of preserving and presenting as often as is needed, a controlled stimulus pattern of flickered light, or of other sensory modalities, in various research applications.

SUMMARY

It is suggested that inconsistencies in the effectiveness of intermittent photic stimulation as an EEG activation technique in the same laboratory and in different laboratories are, in part, the result of a widely varied programming of the photic stimulus by the technician applying the test. It is also pointed out that a need exists for programmed stimuli to enable critical evaluation of cerebral sensitivity to light both for diagnostic and therapeutic purposes. Hitherto, in many instances, it has been impossible to evaluate whether certain changes in light sensitivity as recorded on the electroencephalogram were ascribable to the patient or to the technique. Standardized testing is also required in order to effectively screen members of families in the study of genetic cerebral light sensitivity, as well as cerebral light sensitivity arising from other causes and to detect light-sensitivity in individuals in order to exclude them from hazardous occupations, e.g., helicopter pilots, recruits, public transport operators, etc.

To this end a *Stimulus Program Unit* and ferromagnetic tape *Stimulus Test Programs* have been developed. The unit is simple to operate and highly reliable. The programs may be prepared in advance for mass screening purposes or prepared, at the time of the initial EEG examination, for individual cases. The unit and programs are considered to be a prerequisite for any precise studies on the detection, treatment and investigation of cerebral light sensitivity.

REFERENCES

CHANCE, B. Waveforms. *Rad. Lab. Series*, **1949**, *19*: 166-171. McGraw Hill New York.

DAVIDSON, S. and WATSON, C. W. Hereditary light sensitive epilepsy. *Neurology*, **1956**, *6*: 235-261.

HUNTER, J. and WATSON, C. W. **1958**. Unpublished data.

PUCKLE, O. S. *Time Bases*. Pub. John Wiley & Sons, Inc., New York, **1955**, pp. 53 and 81.

SCHMITT, O. H. A thermionic trigger. *Journ. Sci. Insts.*, **1938**, *15*: 24.

WALTER, W. GREY, DOVEY, V. J. and SHIPTON, H. Analysis of the electrical response of the human cortex to photic stimulation. *Nature*, **1946**, *158*: 540-541.

Reference: HUNTER, J., WATSON, C. W. and DEGELMAN, J. A method for recording and reproducing programmed stimuli: a basis for accurately evaluating the cerebral electrical response to sensory stimulation. *EEG Clin. Neurophysiol.*, **1959**, *11*: 587-590.

A TRANSISTOR TIMED STIMULATOR [1]

José M. R. Delgado, M.D.
Departments of Physiology and Psychiatry, Yale University School of Medicine, New Haven, Conn.

(Received for publication: August 22, 1958)

Many methods have been devised for electrical stimulation of the brain of unanesthetized, unrestrained animals. In some of them leads were implanted within the brain with terminals outside the scalp that could be connected to appropriate instruments during the experiments. The main limitation of these techniques was that the connecting leads imposed some restriction of movement. However, they have been successfully used by many authors (Hess 1932; see reviews in Delgado 1955, 1958a).

To avoid any disturbing manipulation of the animal during stimulation other methods were developed, based on remote control activation of a small implanted receiver (Chaffee and Light 1934; Clark and Ward 1937; Fender 1937; Gengerelli and Kallejian 1950; Harris 1946; Loucks 1934; Verzeano and French 1953). The absence of connecting leads and of skin trauma was an advantage, but some handicaps should be mentioned: in general only one cerebral point could be studied and direct recording of brain electrical activity was not possible. Also in some cases the need to orientate the secondary coil implanted in the animal, with respect to the primary, imposed a greater restriction on the subject's movements than the connecting leads had done. There was still another problem, common to all remote control methods, including the radio frequency carriers: *the intensity of brain stimulation depended upon the intensity of the received signal.* Changes in the orientation of the receiving antenna, the distance from the emitting source, obstacles between the two (such as another animal), etc., could change the intensity of brain stimulation in some unpredictable way. Since it was not possible to monitor the stimulation, voltage and amperage could not be measured.

A new approach to these problems led to the construction of the transistor timed stimulator [2] which is the subject of this paper. First, 12 to 24 leads were implanted in each monkey. The terminal sockets emerged from the scalp at the back of the head, according to a previously described technique (Delgado 1952, 1955). After the skin around the implanted electrodes had healed (1-2 weeks) subcutaneous leads made of stainless steel, .07'' diameter, insulated by quadruple teflon, were introduced between the base of the socket and the back of the neck. A #22 intramuscular needle was used to pass the leads under the skin, a procedure as simple as giving an injection. A tiny stimulator attached to a collar was then put on the monkey and connected by the subcutaneous leads to any chosen terminals of the intracerebral electrodes. Three problems were solved in this way: (i) we could explore many cerebral areas; (ii) we could monitor the stimulations from time to time, using connecting leads between monkey and oscilloscope; (iii) we could register the electrical activity of the brain (with the animal under some restraint).

The transistor stimulator. Several electronic attemps to avoid changes in stimulation output produced by changes in the received signal, failed, and a mechanical electronic solution was found (see fig. 1, 2, 3). A multivibrator was constructed with two CK822 junction transistors running at a frequency of 100 c/sec. The waves were rectified through a diode (IN34) and the output, between 0 and 20 V., was controlled by a 5,000 ohm potentiometer which was the only dial on the instrument and could easily be adjusted by hand. The shape of the pulses was exponential fall as shown in figure 2, with a pulse length of 0.05-0.1 msec. Power was provided by a 22½ V. battery (Burgess Y15); on a few occasions a 30 V. battery was used. All parts were subminiature and the total size of the instrument was only 3 x 1½ x 1 cm.; the separately mounted battery

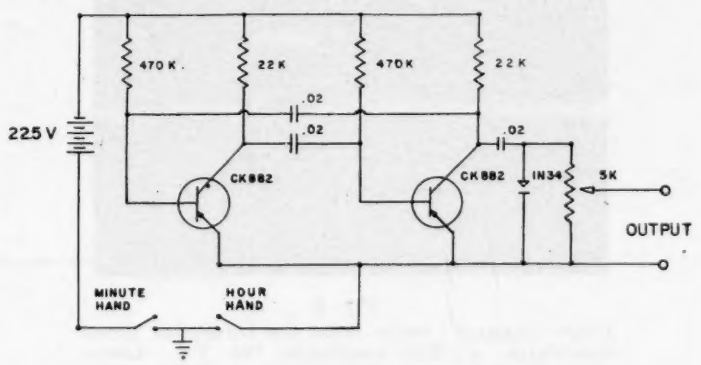


Fig. 1
Diagram of the transistor timed stimulator.

1 This research was supported by grants from The Foundations' Fund for Research in Psychiatry, the United States Public Health Service, and the Office of Naval Research 609(08). Reproduction in whole or in part is permitted for any purpose of the United States Government.

2 The transistor timed stimulator may be ordered from Mr. R. G. Williams, Blue Hills Road, North Haven, Conn.

measured 5 x 1½ x ½ cm. The stimulator, tested in 15 monkeys, was shockproof and gave reliable stimulations.

The battery was connected to the stimulator through a timing device constructed within a small shock resistant wristwatch. Tiny wheels of plexiglas with a small contact in the axis were inserted into the pivots of the second and hour hands. One contact was calculated for 5 sec. and the other for an hour. Whiskers of piano wire established each contact with "ground" in the watch. In this way any of the following stimulations could be programmed: (i) 5 sec. of stimulation every minute for 1 hour every 12 hours; (ii) 5 sec. of stimulation every minute continuously; (iii) one hour of continuous stimulation with predetermined beginning and end; (iv) continuous stimulation. By changing the size of the contacts in the plexiglas wheels a great variety of stimulation program could be established.

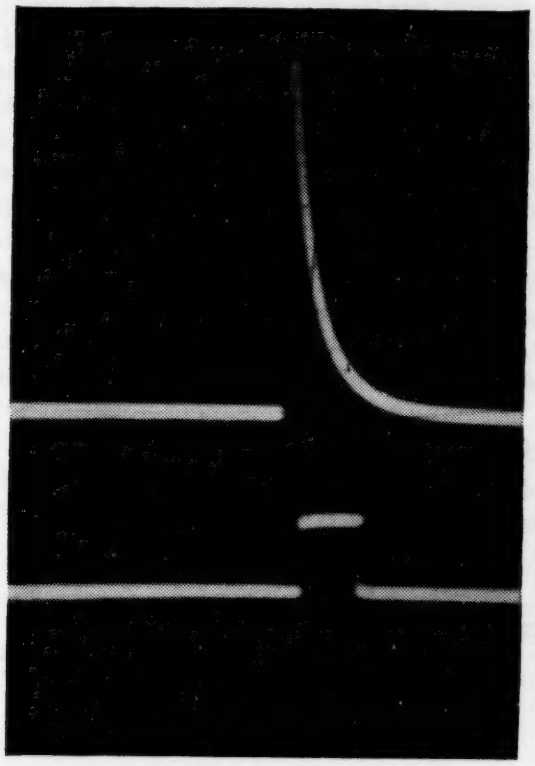


Fig. 2
Upper channel: pulse from the transistor timed stimulator, at full amplitude (20 V.). Lower channel: 0.1 msec. pulse from a Grass stimulator.

The routine was as follows: the monkey with implanted cerebral electrodes and a dummy collar ran free in its cage. Before the experimental day the animal was lightly restrained and all the cerebral contacts were tested with the transistor stimulator and monitored by an oscilloscope. Thresholds and effects were noted. The next day the collar stimulator was put on instead of the dummy, voltage and timing were set, and selected cerebral points connected. The monkey was then returned to its cage where programmed stimulation started one or several hours later, and we could observe or photograph the evoked effects.

For the past years we have successfully used this method, especially to study the effects of brain stimulation upon social behavior, recorded by time-lapse photography.

Fig. 3
Transistor timed stimulator attached to monkey's collar.

A monkey wearing the stimulator is shown in figure 3. The timer is visible on the left side of the neck and the stimulator is the small object on the upper part of the collar. The animals usually became accustomed to the dummy collar and later did not tamper with the stimulator. The other animals might be curious about it for a while but they proved to be very considerate. We have seen them grooming each other, and gently lifting the collar to reach the skin underneath without paying much attention to the stimulator; the instrument gradually seemed to be considered part of the animal. Results obtained with this device will be published elsewhere (Delgado 1958b).

SUMMARY

Our technique of permanently implanted electrodes, combined with a miniature transistor stimulator and a timing device, permitted a well controlled electrical stimulation of the brain in monkeys with unlimited freedom of the animals.

The physical characteristics of the pulses were unidirectional exponentially falling waves of 100 c/sec. pulse duration of 0.05-0.1 msec., varying from 0 to 20 V.

Reference:

With this method many cerebral areas could be explored in the free subject, and by using some restraint it was possible to monitor the stimulation by oscilloscope and to record the electrical activity of the brain.

I should like to thank Mr. R. G. Williams, for his skillful collaboration and ingenuity in the development and construction of the instrument. I should also like to thank Dr. Junji Ushiyama and Mr. Was Litvenko for their help in some of the electronic problems, and Dr. Harold Lamport for our useful discussions.

REFERENCES

CHAFFEE, E. L. and LIGHT, R. U. A method for the remote control of electrical stimulation of the nervous system. I. The history of electrical excitation. *Yale J. Biol. Med.*, **1934-35**, *7*: 83-128.

CLARK, S. L. and WARD, J. W. Electrical stimulation of the cortex cerebri of cats: Responses elicited in chronic experiments through implanted electrodes. *Arch. Neurol. Psychiat.*, Chicago, **1937**, *38*: 927-943.

DELGADO, J. M. R. Permanent implantation of multilead electrodes in the brain. *Yale J. Biol. Med.*, **1952**, *24*: 351-358.

DELGADO, J. M. R. Evaluation of permanent implantation of electrodes within the brain. *EEG Clin. Neurophysiol.*, **1955**, *7*: 637-644.

DELGADO, J. M. R. Chronic emplacement of intracerebral electrodes. *Proc., Symp. on Brain Stimulation*, Houston, ed. D. Sheer (in press), **1958**a.

DELGADO, J. M. R. Prolonged stimulation of the brain in awake monkeys. (Submitted for publication) **1958**b.

FENDER, F. A. Epileptiform convulsions from "remote" excitation. *Arch Neurol. Psychiat.*, Chicago, **1937**, *38*: 259-267.

GENGERELLI, J. A. and KALLEJIAN, V. Remote stimulation of the brain in the intact animal. *J. Psychol.*, **1950**, *29*: 263-269.

HARRIS, G. W. The innervation and actions of the neurohypophysis; an investigation using the method of remote-control stimulation. *Philos. Trans.* (Roy. Soc. Lond.), **1946-47**, *232B*: 385-441.

HESS, W. R. *Beiträge zur Physiologie des Hirnstammes.* I. *Die Methodik der lokalisierten Reizung und Ausschaltung subkortikaler Hirnabschnitte.* Leipzig, Georg Thieme, **1932**, 122 pp.

LOUCKS, R. B. Technique for faradic stimulation of tissues beneath the integument in the absence of conductors penetrating the skin. *J. comp. Psychol.*, **1934**, *18*: 305-314.

VERZEANO, M. and FRENCH, S. D. Transistor circuits in remote stimulation. *EEG Clin. Neurophysiol.*, **1953**, *5*: 613-616.

Reference: DELGADO, J. M. R. A transistor timed stimulator. *EEG Clin. Neurophysiol.*, **1959**, *11*: 591-593.

PRINTED IN GREAT BRITAIN

SIMULTANEOUS TWO CHANNEL FREQUENCY ANALYZER WITH NON-ELECTRONIC (PASSIVE) FILTERS [1]

MELVIN MEISTER, ROBERT S. SCHWAB, M.D., ELIZABETH PETERSEN, B.A. and ALBERT GRASS, B.S.

Electroencephalographic Laboratory, Massachusetts General Hospital, Boston, Mass.

(Received for publication: August 23, 1958)

After 10 years experience with the Walter type of single channel electronic wave analyzer we felt the need of a more practical and useful, and perhaps less complicated, electronic device for use in a clinical EEG Laboratory. In spite of better vacuum tubes and circuits there still is some instability of the vacuum tube tuned oscillating circuits. We felt the restrictive requirements of analysis of only one 10-sec. epoch to 2 electrodes (one channel) every 30 sec. made check of any analysis against two other points too difficult. Finally, the demand of such an instrument for proper performance on the constant presence of an experienced electronic engineer for maintenance led us to look for an instrument with the following characteristics:

(1) The filter or tuned element would be a passive (non-electronic) capacitor-inductive sealed network of constant stability never requiring tuning or adjustment.

(2) There would be simultaneous write-out of the analysis of two channels at all times so a check of one analyzer against its mate would be as easy as a voltage calibration of any two channels.

(3) The write-outs would be directly over the primary trace of the channel being analyzed eliminating the need of a channel marker.

(4) The frequency bands analyzed would be limited to those of direct clinical interest (eight for each channel) and changing these would be possible by simply plugging in other filter elements without requirements of extensive adjustments, tuning, or replacing of circuit elements.

(5) The duration of the so-called epoch could be altered by one switch control from as short as 4 sec. to as long as 1 min.

(6) One switch would control the pre-filter amplifiers so a single write-out would indicate overloading.

(7) It is hoped that when fully developed it will not require the constant services of an electronic engineer.

---

1 Read at the annual meeting of the American Electroencephalographic Society, Atlantic City, June 14, 1958.

The Twin Channel Frequency Analyzer consists of two identical channels with each channel analyzing eight frequency bands. The analyzer provides information that approximates the Fourier Analysis of the complex EEG wave form.

THE FILTERS

These were especially designed and constructed. They are absolutely stable with temperature changes, vibration, continued use or excessive transients. They cover a full cycle with flat top and only spread into adjacent bands by 10 per cent.

The frequency sensitive units are simple passive resonant circuits with a constant Q of 7.5. The coils were wound on cores of hypermaloy ultrathin gauge 79 per cent nickle alloy and while no attempt at miniaturization was made in this prototype it is predicted that both size and cost will compare favorably with electronic units. Their maximum responses occur at 5.4, 6.1, 7.0, 8.0, 9.1, 10.5, 12, and 13.6 cycles per second. The response of each filter is down 70 per cent at a frequency midway between its maximum response frequency and the maximum response frequency of the adjacent filter. The adjacent channel response to a signal occurring at the maximal response of the filter is 10 per cent. The variation of the maximum response frequency of the

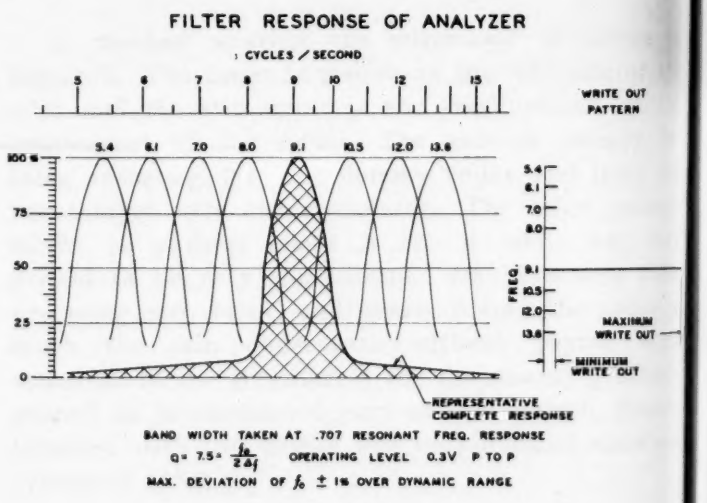


Fig. 1. (See text).

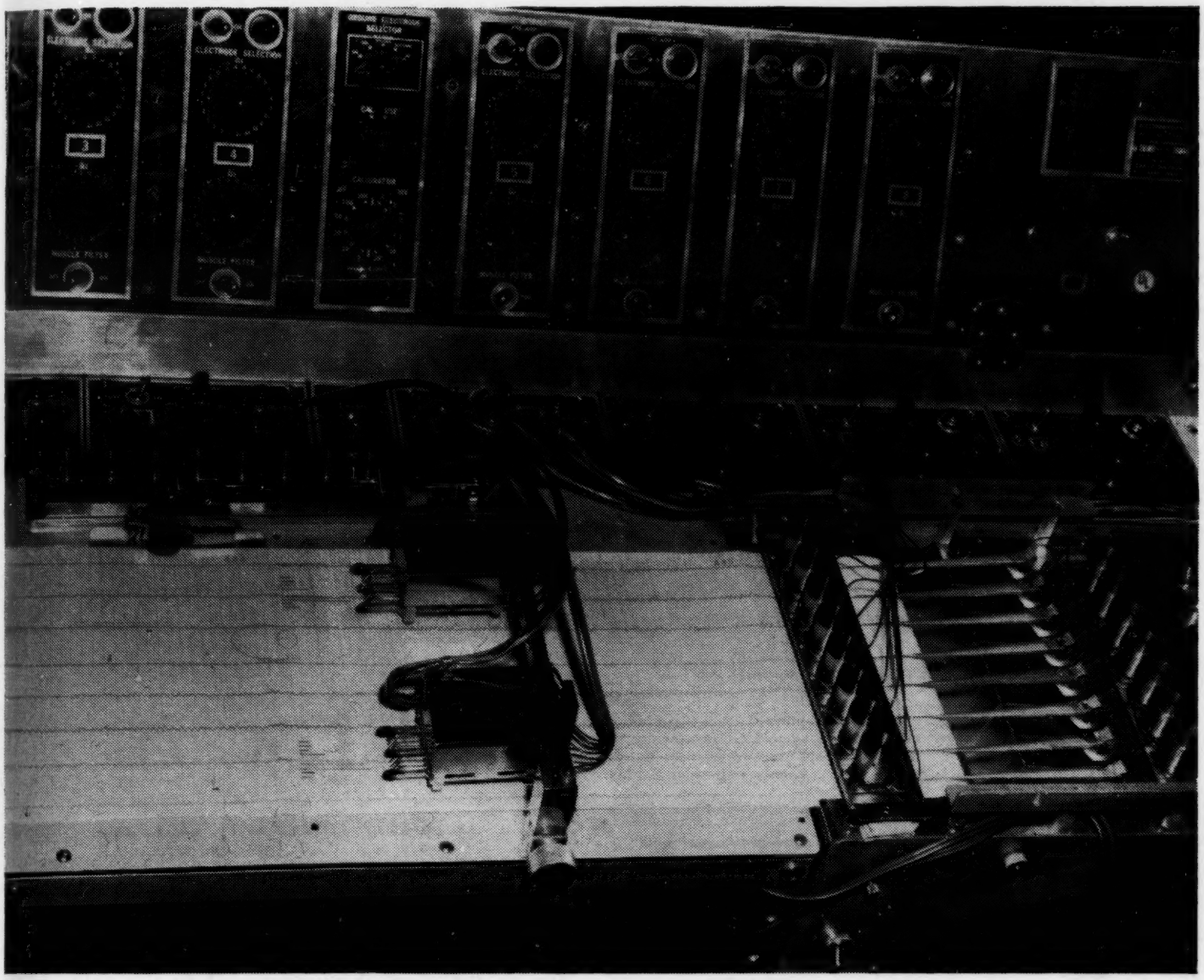


Fig. 2. (See text).

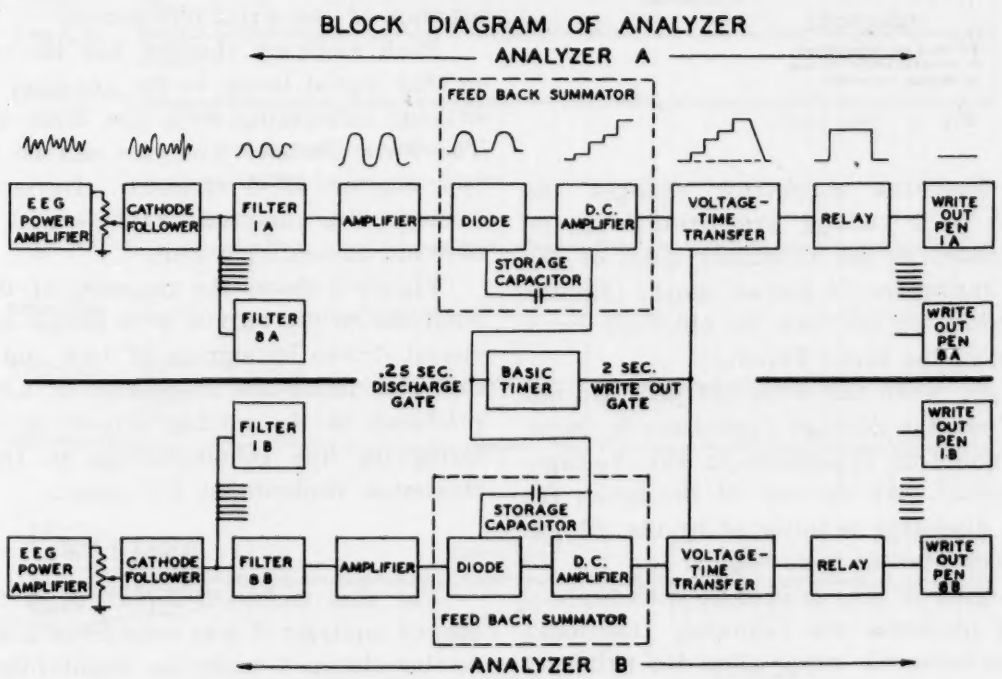


Fig. 3. (See text).

filters is no greater than 1 per cent over the dynamic operating range. The filters are stable and require no adjustment.

Figure 1 shows the graph of the amplitude-frequency characteristics of the filters with one representative response curve completed.

The write-out display for each analyzer channel is an eight line histogram written directly over the EEG record in the channel being analyzed. The length of each line of the histogram on the time axis of the EEG chart is proportional to the energy in the corresponding frequency band. The analyzer writes out at the end of each epoch, but the write out unit is physically displaced (see fig. 2) so that the display appears at the beginning of each epoch on the EEG record.

Epoch time, write out time and reset time of both analyzer channels are controlled by the Basic Timer which produces gating pulses of 10, 2 and .25 sec. respectively.

The output from each filter is amplified and presented to the corresponding Feedback Summator

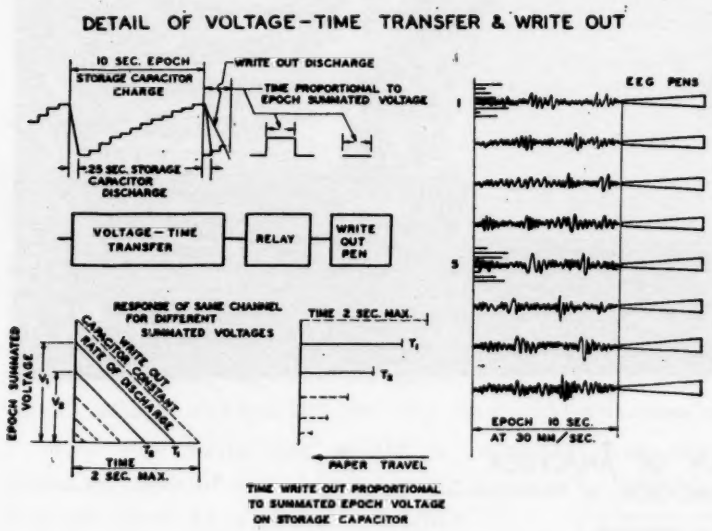

DETAIL OF VOLTAGE-TIME TRANSFER & WRITE OUT
10 SEC. EPOCH
STORAGE CAPACITOR CHARGE
WRITE OUT DISCHARGE
TIME PROPORTIONAL TO EPOCH SUMMATED VOLTAGE
.25 SEC. STORAGE CAPACITOR DISCHARGE
VOLTAGE-TIME TRANSFER
RELAY
WRITE OUT PEN
EEG PENS
RESPONSE OF SAME CHANNEL FOR DIFFERENT SUMMATED VOLTAGES
EPOCH SUMMATED VOLTAGE
WRITE OUT CAPACITOR RATE OF DISCHARGE CONSTANT
TIME 2 SEC. MAX.
TIME 2 SEC. MAX.
PAPER TRAVEL
TIME WRITE OUT PROPORTIONAL TO SUMMATED EPOCH VOLTAGE ON STORAGE CAPACITOR
EPOCH 10 SEC. AT 30 MM/SEC.

Fig. 4. (See text).

(fig. 3). The Feedback Summator changes the Storage Capacitor to a voltage proportional to the total energy contained in the frequency band of the associated filter, during the 10 second epoch. (Epochs of more or less than 10 sec. can be obtained by a simple adjustment of the Basic Timer.)

During the 8 sec. when the write out pens are not writing, energy from the Storage Capacitors is transferred to the Write Out capacitors in the Voltage-Time Transfer circuit. At the end of the epoch the storage capacitor discharge is initiated by the .25 sec. reset gate and a new storing cycle begins.

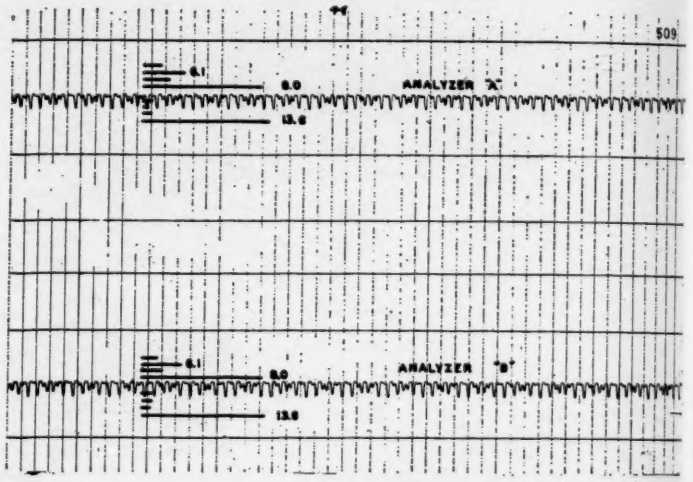
The write out gate is also coincident with the end of an epoch and performs the following functions:

1. Operates the Solenoids which allow the write out pens to contact the chart paper.

2. Clamps the voltage on the write out capacitors so no further storage will occur during the write out period.

3. Permits the linear discharge of the write out capacitors in the Voltage-Time Transfer circuit (fig. 4).

During the write-out period the write-out capacitors are discharged at a constant rate providing a linear voltage time relationship as shown in figure 4. This linear voltage slope is sampled by a voltage comparator which operates the pen lifting solenoid when the discharge voltage reaches a predetermined value. As the chart speed is constant and the relation



RESPONSE OF ANALYZER TO 13.9 AND 8.0 C.P.S. MIXED IN A SIMPLE NONLINEAR NETWORK (WHICH ALSO PRODUCES SUM & DIFFERENT FREQUENCIES AND HARMONICS)

Fig. 5. (See text).

of time to discharge voltage is linear, the length of the line on the chart is proportional to the value of the voltage stored on the write-out capacitor at the beginning of the write out period.

Each analyzer channel has its own gain control so that signal levels to the analyzer can be adjusted without interfering with the EEG trace calibration. The Twin Channel Analyzer can be driven from any two selected EEG channels. Deviation in write-out between two analyzed channels with identical inputs does not exceed 5 per cent.

Figure 5 shows the response of the Twin Channel Analyzer to the output of a simple non-linear mixing circuit driven by signals of 13.9 and 8.0 c/sec. Note that the difference frequency of 5.9 c/sec. which is produced in the mixing circuit is indicated in the histogram line corresponding to the filter with a maximum response at 6.1 c/sec.

RESULTS

For this technical report of a two channel frequency analyzer it was considered advisable to present results obtained under as standardized conditions as possible in order to better evaluate the performance

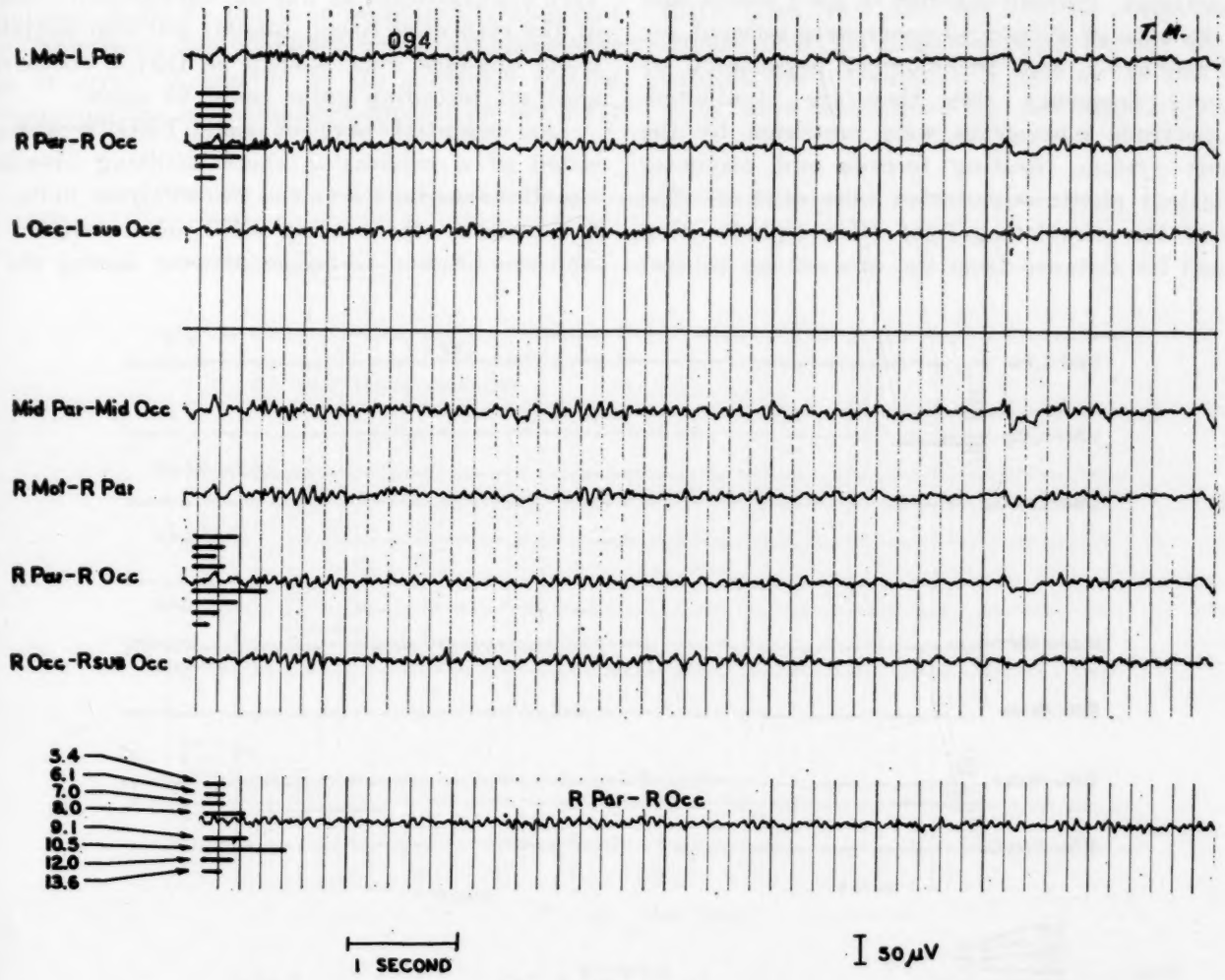


Fig. 6. (See text).

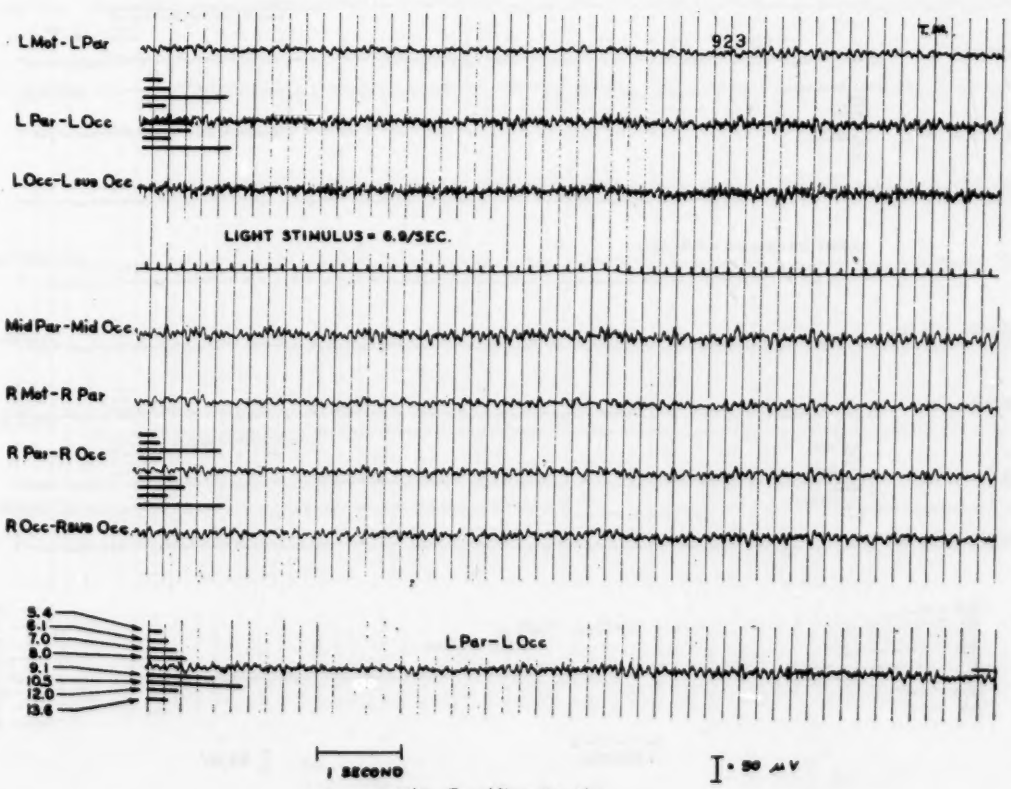


Fig. 7. (See text).

of the apparatus. Normal controls in good health and between the ages of 20 and 40 years were selected for study. Presumably any pathological asymmetry of voltage and frequency was therefore eliminated. Surface electrode placements were measured by the Ten-Twenty system. Resting records and responses to intermittent photic stimulation were studied. The intensity of the stimulating light (Grass photo stimulator) and its distance from the eyes of the subject were kept constant as was the background illumination of the recording room. Similar parietal-occipital electrode linkages were studied so that a comparison of analyzer recording gains could be made.

An essential part of each EEG recording consisted of a calibration check utilizing identical and simultaneous inputs to the two analyzer units. Figure 6 represents the resting EEG of a subject (T.M.) who was allowed to become drowsy during the testing

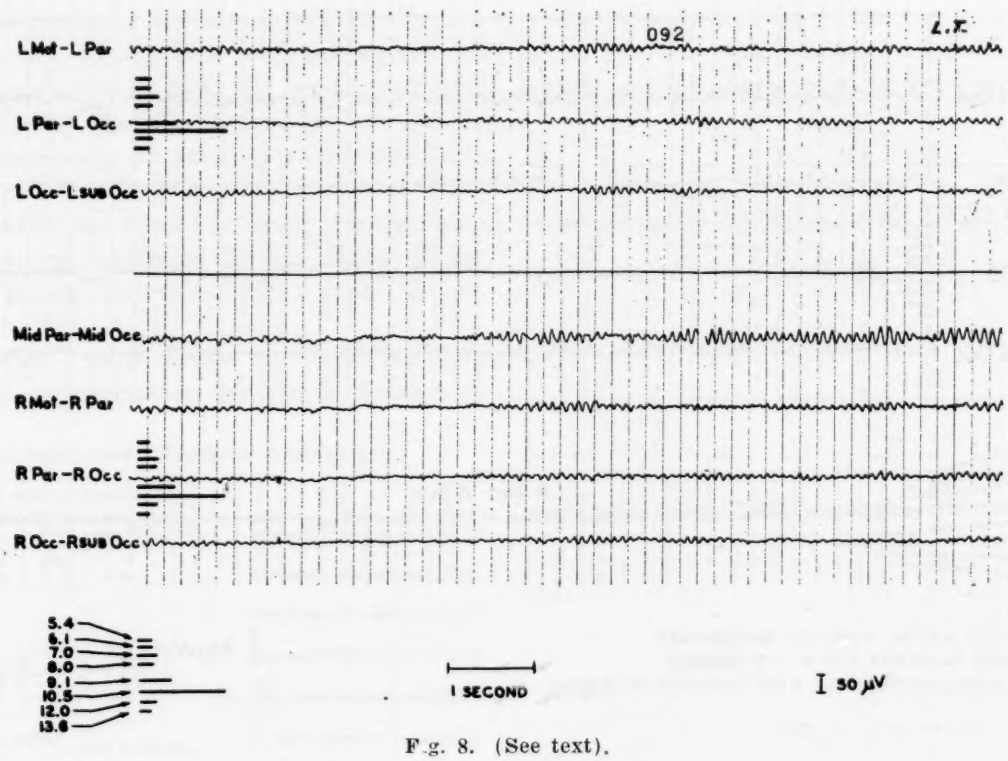


Fig. 8. (See text).

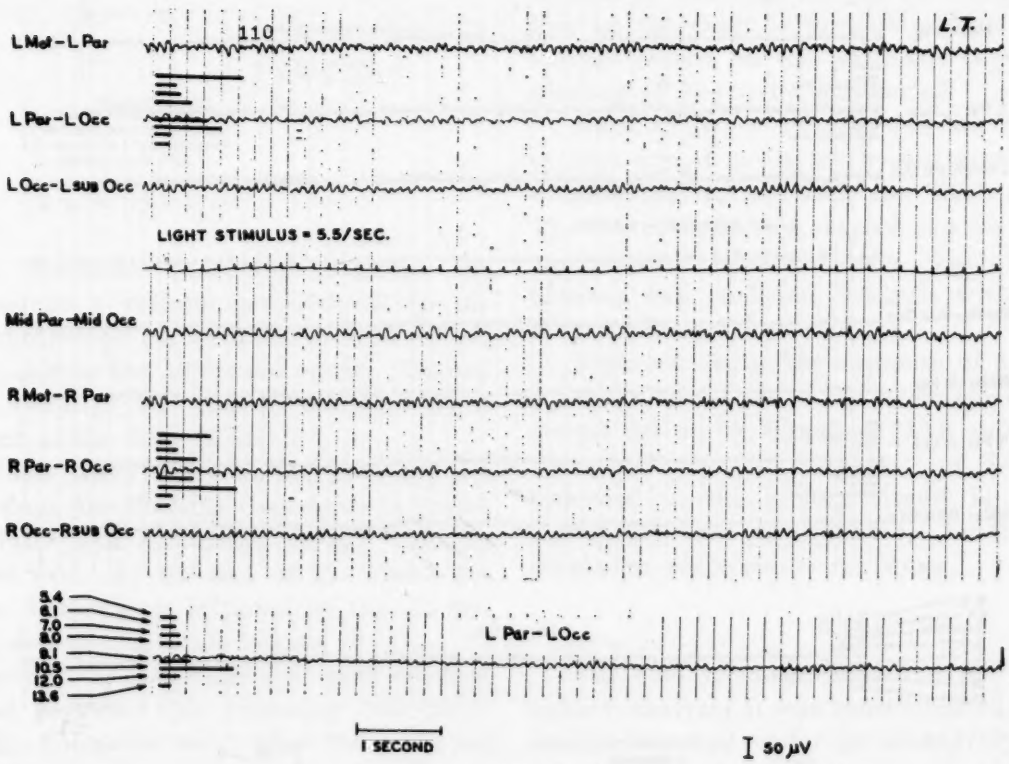


Fig. 9. (See text).

period. Identical electrode linkages were selected for the analyzed channels and it is immediately apparent that the apparatus was operating within an acceptable margin of error. A sample of the subject's waking EEG involving the same linkages appears on the lower section of figure 6 to illustrate the mean frequency shift from 10.5 per sec. to 9.1 and 5.4 per sec. Figure 7 is an analyzed EEG sample of the same subject being flashed at a rate of 6.9 per sec. (flash rates were determined by counting 10 sec. periods,

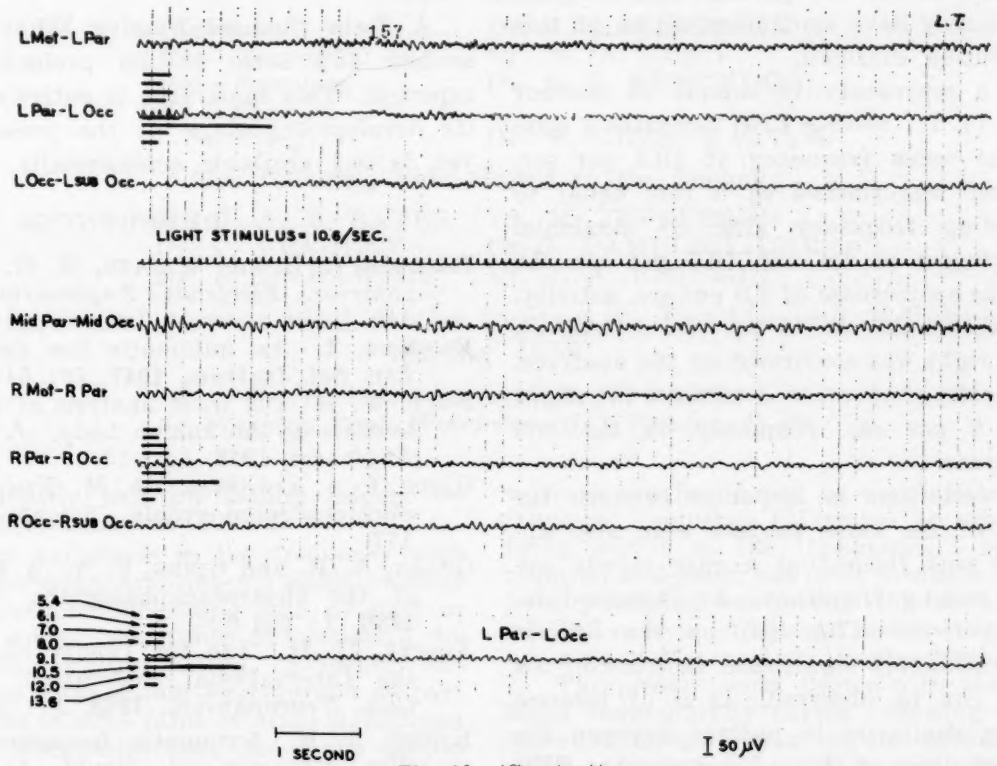


Fig. 10. (See text).

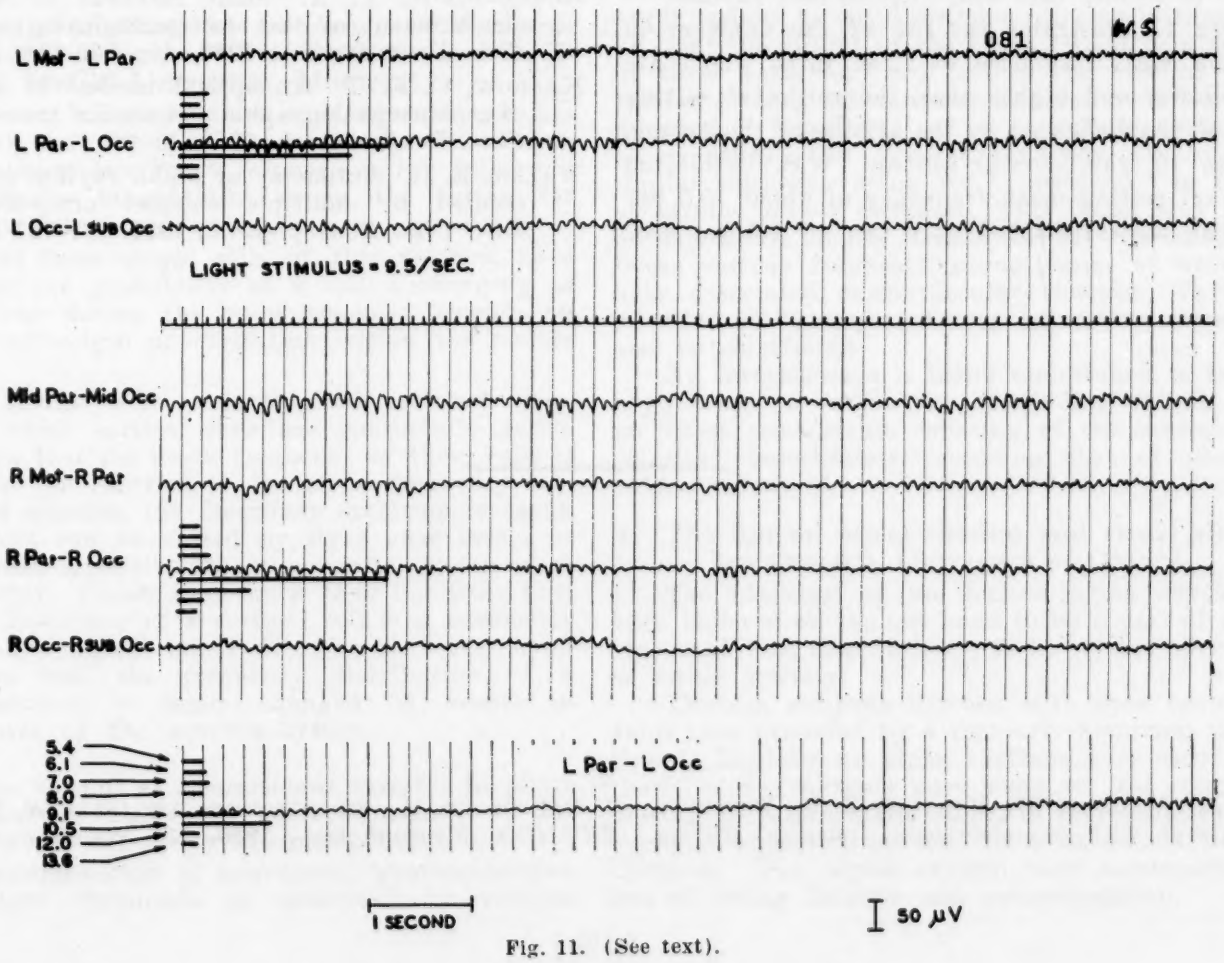


Fig. 11. (See text).

and the subjects' eyes were closed). The analyzer write-outs demonstrate the presence of a symmetrical response at the flash rate and its first harmonic with some residual of the resting frequency, as demonstrated at the bottom of the figure. Muscle artifact involving electrodes on the left parietal and occipital areas would ordinarily have made recognition of this frequency distribution difficult.

In figure 8, a representative sample of another normal subject's (L.T.) resting EEG indicates a symmetrical dominant mean frequency of 10.5 per sec. When this subject was flashed at a rate equal to one-half her resting frequency (fig. 9) maximum responses were present at 5.4 and 10.5 per sec. In addition, there was an increase of 7.0 per sec. activity. The apparent presence of more 5 per sec. activity on the left than the right was confirmed by the analyzer. It would be difficult, however, to determine the slight increase of the 9 per sec. frequency on the left without the analyzer.

These slight variations in responses between the two hemispheres of the same subject were also apparent when she was flashed at a rate closely approximating her resting frequency. An increased response at 10.5 per sec. (fig. 10) on the left in addition to a questionably significant increase of 5.4 per sec. activity can be observed. It is of interest to note the gross similarity in pattern between the resting occipital rhythms of this subject and her EEG response to a flash rate which equals that rhythm.

Figure 11 illustrates the use of the analyzer in evaluating EEG responses to flash rates which are slightly lower and higher than the subjects' resting frequency. As indicated by the sample at the bottom of figure 10, this normal control (W.S.) exhibited a dominant resting mean frequency of about 10.5 per sec. When he was flashed at a rate of 9.5 per sec., there was a bilateral response at this frequency, although an increased component of his resting frequency is more noticeably present on the left than on the right.

CONCLUSIONS

A Twin Channel Passive Filter Analyzer is described and some of its preliminary results are reported. This apparatus is entirely in the midst of its development stage at the present time and, as yet, is not available commercially.

REFERENCES

BALDOCK, G. R. and WALTER, W. G. A new electronic analyser. *Electronic Engineering*, **1946**, *18*: 339-342.

BARBOUR, I. An automatic low frequency analyser. *Rev. Sci. Instrum.* **1947**, *18*: 516-522.

BOYD, W. E. The wave analysis of low frequency potentials of the human body. *J. Brit. Inst. Radio Engineers*, **1948**, *8*: 1-13.

GIBBS, F. A. and GRASS, A. M. Frequency analysis of electroencephalograms. *Science*, **1947**, *105*: 132-137.

GRASS, A. M. and GIBBS, F. A. A Fourier transform of the electroencephalogram. *J. Neurophysiol.*, **1938**, *1*: 521-526.

JASPER, H. H. The ten twenty electrode system of the International Federation. Appendix, *EEG Clin. Neurophysiol.*, **1958**, *10*: 259-278.

KNOTT, J. R. Automatic frequency analysis. *EEG Clin. Neurophysiol.*, Suppl. *4*: **1953**, 17-25.

KOZHEVNIKOV, V. A. Some methods of automatic measurement of the electroencephalogram. *EEG Clin. Neurophysiol.*, **1958**, *10*: 259-278.

KRAKOW, C. E. T. An optical method of analyzing electroencephalographic and similar records. *EEG Clin. Neurophysiol.*, **1951**, *3*: 97.

WALSH, E. G. Autonomy of alpha rhythm generators studied by multiple channel cross-correlation. *EEG Clin. Neurophysiol.*, **1958**, *10*: 121-130.

Reference: MEISTER, M., SCHWAB, R. S., PETERSON, E. and GRASS, A. Simultaneous two channel frequency analyser with non-electronic (passive) filters. *EEG Clin. Neurophysiol.*, **1959**, *11*: 594-600.

PRINTED IN CANADA

SOCIETY PROCEEDINGS

THE EEG SOCIETY

At the Annual General Meeting held on October 4, 1958, the following officers were elected:

Chairman:	Dr. J. R. DAVIDSON
Hon. Treasurer:	Dr. W. A. COBB
Hon. Secretary:	Dr. S. L. SHERWOOD
Hon. Foreign Secretary:	Dr. W. GREY WALTER

The following were elected to the Council:

Dr. J. A. V. BATES	Dr. M. JEFFERSON
Dr. P. BRADLEY	Dr G. PAMPLIGLIONE
Dr. G. D. DAWSON	Dr. J. A. SIMPSON

Summaries of papers read at the Centres in London and Edinburgh during 1958

Proceedings Secretary: Dr. G. PARR
68, Compton Road, Winchmore Hill, London, N. 21

1. The sudden bodily jerk on falling asleep. — Ian Oswald, University of Oxford.

There are large variations in the frequency with which different individuals experience a sudden violent and momentarily rather frightening jerk of part or the whole of the body (sometimes accompanied by hallucinations) when falling asleep. Evidence was presented that these jerks should be regarded as part of an arousal process to some faint external significant sensory stimulus. The claim that the jerks should be regarded as epileptic was critically considered.

2. Factors controlling the frequency of discharge of cortical neurones. — B. D. Burns and G. K. Smith, McGill University, Montreal.

In the cat's anaesthetized isolated cortex, it has been shown that there is a network of cells capable of transmitting the burst response which follows a single stimulus tangentially across the cortex for very large distances.

Records from single cells of this network have shown that the probability of a cell discharging at various times during the burst response depends on the point of origin of excitation within the isolate network.

Experiments with unaesthetized isolated forebrain in which cortical cells are continually active have shown that the mean frequency of these cells is very stable. In contrast to the mean frequency recorded over minutes, the frequency spectrum is easily changed and can be varied by light anaesthesia or by very weak repetitive stimuli given to remote areas of the cortex. Preliminary work thus indicates that the mean frequency of a cortical cell is a parameter of little physiological importance; on the other hand it appears that the frequency distribution of a cortical neurone is easily changed by events in remote parts of the nervous system.

3. Cardiac output as a significant variable in pharmacological "threshold" determination. — M. V. Driver, Maudsley Hospital, London.

The determination of convulsive, photoconvulsive and sedation thresholds as practised by various workers can be likened to a volumetric titration, the ''known'' solution (Metrazol or other active drug) being added to the ''unknown'' system until the required end-point has been attained. Much work has been published concerning the suitability or otherwise of various end-points and the significance of the amounts of Metrazol etc. to give them.

The present work began with the deduction that blood radio-activity curves following the injection of radio-iodinated human serum albumen solution — which demonstrate marked variations in peak and mean concentration from patient to patient — must apply equally to any substance injected intravenously, i.e. that the output of the heart (which is a function of these variables) will affect the arterial concentration of that substance and therefore influence the apparent ''threshold'' of a convulsant, sedative or other drug. The general tendency (in otherwise similar subjects) being for ''threshold'' to increase as cardiac output increases. This factor may also be of importance in the comparison of ''threshold'' between various diagnostic groups, some of which may have associated cardiovascular changes. Variability of effect of the injected drug on cardiac output may also be significant.

An investigation is being undertaken to test this hypothesis, an estimation of cardiac output (based on direct scintillation counting of the cardiac radioactivity) immediately preceding that of photo-convulsive threshold.

4. The human alpha rhythm and visual alertness. — Ian Oswald, University of Oxford.

The blocking of the human alpha rhythm has been believed on the one hand to be a part of general ''arousal'' or, alternatively, to be related specifically to visual activity.

Thirteen subjects listened with eyes open for a faint tone preceded by a regularly recurring warning signal. Initially no alpha rhythms were seen. Eventually alpha rhythms were more or less continuous. During an intermediate stage, in five subjects, alpha rhythms appeared at the times of intent auditory alertness. The alpha rhythm was accompanied by loss of ocular fixation and accommodation.

It is proposed that alpha blocking represents increase of specific visual alertness which may be but one component of general arousal. Specific auditory alertness may be accompanied by reciprocal inhibition of visual functions, at the periphery, during transmission, and centrally.

5. Electroencephalographic studies in the syndrome of relative cerebral hypoglycaemia. — Barry D. Wyke, Neurosurgical Centre, Woolwich.

Relative cerebral hypoglycaemia is a recently described syndrome characterized by a disturbance of cerebral carbohydrate metabolism such that arterial glucose concentrations, adequate in most subjects for normal cerebral function, are insufficient to meet the metabolic requirements of the brains of patients. These requirements can, however, be satisfied at blood glucose levels well above those needed in normal subjects.

Whenever the blood glucose level falls below the abnormal high levels necessary for normal cerebral metabolism in patients with *relative* cerebral hypoglycaemia, they display many of the symptoms produced by *absolute* hypoglycaemia in normal subjects. Thus headache, confusional states, disorders of behaviour, unconsciousness, and motor, sensory and visceral seizure phenomena occur episodically as ictal disturbances in cases of relative cerebral hypoglycaemia.

In the fasting state, patients with relative cerebral hypoglycaemia display marked electroencephalographic abnormalities (including paroxysmal discharges) in association with the symptoms described, even though their blood glucose concentrations remain between 70 and 100 mg/100 ml. These electrical and clinical abnormalities diminish and finally disappear as the blood glucose level rises after ingestion of glucose — but not until concentrations as high as 160 mg/100 ml. are reached. As the ingested glucose is removed from the blood the disturbances of cerebral function gradually reappear at the rate of the fall in glucose concentration of the blood.

6. Clinico-electroencephalographic study of frontal gliomata. — M. Fischer-Williams and G. Lyberi, London Hospital.

In this paper 35 cases of frontal glioma taken from a series of 102 gliomata and 46 intracranial metastatic tumours are studied, the diagnosis having been verified histologically in 32 of these patients. In a further two the tumour was seen at operation but biopsy was considered inadvisable. The record nearest histological verification was analysed and classified.

It was found that in one third of the cases of frontal tumours the slow wave activity was regular, in contradistinction to the irregular slow activity with gliomas in other situations. The slow wave activity was often of high or very high voltage and tended to be episodic. Thus half the slow wave discharges were episodic, whereas out of 52 cases of temporal and parietal gliomas only 6 were episodic and the great majority were continuous. In almost one third of the cases of frontal glioma there was well preserved background activity as opposed to the more widespread disturbances seen in gliomata in other situations; this is in part an expression of the lessened degree of disturbance of the alpha rhythm in frontal tumours. In nearly a quarter of the frontal gliomas the EEG showed a non-localizing abnormality, such as unilateral slowing of the alpha rhythm, or generalized bilateral slowing of cerebral activity, or (in 1 case) a normal record. In nearly half the frontal gliomas the slow wave discharge was bilateral, mainly bifrontal: this contrasts with the fact that out of 52 temporal and parietal tumours in only 4 was the slow activity bilateral.

7. Correlation between EEG pattern, excitement and ventricular fluid protein level. — J. P. Farrel and S. L. Sherwood, Severalls Hospital, Colchester, Essex.

Termination of status epilepticus by lumbar puncture is a well known clinical procedure; when ventriculograms were carried out on epileptics it was noticed that the frequency of fits diminished and that they became better behaved for three or four weeks. In these cases the C.S.F. protein is often raised.

We have reviewed fifty five ventricular protein levels and in fifty one of these correlated the level with the EEG pattern. In the great majority of cases the EEG was taken within a fortnight of performing ventriculography.

Case material: Ventriculography was carried out for either diagnosis or prior to stereotaxy. The rest was obtained during the course of intraventricular injections: these cases were nearly all schizophrenics.

Protein levels were estimated comparing the turbidity, produced by sulphosalicylic acid, against standards, the normal ventricular protein level being 10-15 mg/ml. If the patients' C.S.F. protein levels are arranged in a descending order the highest incidence of habitual excitement is seen to fall within the range of 25-50 mg/ml.

In the EEG records of all these cases raised protein correlates with excessive amounts of fast and slow activity with an increased incidence of complex wave forms and a reduction of activity within the alpha band, and that the increase of activity within the beta band is not solely due to sedatives.

In view of these results, in two recent cases of so-called temporal lobe epilepsy, after a stereotaxic recording an anastomosis was effected by means of a short length of silicone rubber tubing connecting the temporal horn of the lateral ventrical to the subdural space, the intent being to cause a dilution of the protein by increasing the turnover. In the eight or ten weeks since operation both patients have displayed marked improvement both with respect to seizure incidence and behaviour abnormalities.

8. The clinical and EEG findings in epilepsy of the parasagittal areas. — W. A. Kennedy, Maudsley Hospital, London.

The clinical features to be expected in epilepsy arising from the parasagittal areas are discussed with particular attention paid to epilepsy originating in the supplementary motor area.

Tükel and Jasper's paper (*EEG Clin. Neurophysiol.*, **1952**, *4*: 481-494) is reviewed. They state that the commonest finding is bilaterally synchronous paroxysmal rhythmic discharges, often of an irregular spike and wave form, with frequencies of 2-4 per sec.

The clinical and EEG findings in eight patients, 7 confirmed at operation, are described. None showed any secondary bilateral synchrony — the majority showed spike foci. Among the clinical features sug-

gesting an origin in the parasagittal areas are visceral and genital sensations, sensory motor phenomena of the lower limb particularly involving the foot bilateral movements with little or no disturbance of consciousness. Secondary bilateral synchrony is not so common as was formerly suggested.

9. The EEG in chronic subdural haemotamata. — J. H. D. Millar, Royal Victoria Hospital, Belfast.

The pre-operative records of 23 patients suffering from chronic subdural haematomata are reviewed and an attempt made to relate the abnormality with the patients' clinical state and findings at operation.

The records were normal in 3 patients who had a normal level of consciousness and symptoms of longer duration than 2 months. The haematomata in these were relatively small. An asymmetry of the alpha rhythm was found in 8 records and in 7 the haematoma was on the side of the lower amplitude. Unilateral slow activity was found in 10 records. Haematoma was on the side of the slow activity in 8 and in the 2 incorrect records an alpha asymmetry would have guided to the correct lateralization in one. However, when there was bilateral slow activity as in 10 records, the haematoma was on the side of the low amplitude slow activity in 5, on the other side in 2 and of equal amplitude in 3. An alpha asymmetry would have lateralized the haematoma in the 2 incorrect records and also in one record where the slow activity was bilateral and of equal amplitude. Using this method it was possible, in retrospect, to give a correct lateralization in 16 out of 18 records in which an asymmetry was present in the EEG.

In general the more marked the alteration of consciousness the more abnormal the EEG.

10. Some EEG observations in children soon after head injuries. — G. Pampiglione and K. Till, Hospital for Sick Children, London.

Of a number of children admitted with recent head injuries under the care of W. McKissock, 42 were referred as emergencies to the EEG Dept. and records were taken soon after admission and thereafter at various intervals during the first fortnight.

These patients had closed head injuries, usually without fracture of the skull vault, and remained unconscious from a few minutes to several days.

The severity of the EEG abnormality was not usually an indication for surgical intervention. No satisfactory EEG criteria could be found to suggest the presence or absence of a subdural haematoma.

Some cases were mentioned where the history of recent head injury masked the presence of other cerebral lesions.

11. Long term EEG and ECG studies of young rats, pigs and dogs. — G. Pampiglione, B. S. Platt and R. J. C. Stewart, National Institute for Medical Research, London.

At weekly intervals parallel observations were made on young rats, pigs and dogs during normal development and after nutritional stresses. In addition to various biological, chemical and radiological studies, EEGs and ECGs were taken on 30 rats, 17 pigs and 22 dogs, a total of 303 records. Some of the problems encountered and some of the techniques used to obtain scalp EEGs during waking state and spontaneous sleep were described. The effect of natural sensory stimuli during spontaneous sleep was discussed together with the changes induced by barbiturates.

12. Discrimination and response to stimulation during sleep. — Ian Oswald, Anne Taylor and Michel Treisman, University of Oxford.

In an initial experiment with a volunteer a conditioned emotional arousal response was established to the middle of three tones of 530, 690 and 790 c/sec. When the tones were presented in his sleep, a significantly greater proportion of K-complexes occurred as response to the "important" tone.

In order to test the belief that an individual may arouse especially to his own name it is essential to eliminate the factor of novelty of type of stimulation. A tape recording was made of 56 names, spoken urgently, in alternating male and female voices, at intervals of 5, 7, 4, 8 and 6 sec., each name occurring many times in all, and also with a series of names spoken twice at one time. Sleep-deprived volunteers fell asleep while the tape was being played, having been instructed to make a fist to their own and a control name.

Some subjects failed to respond overtly to the names as soon as they became drowsy. Others, however, have shown a remarkable capacity to wake up from sleep to their own name, the latter being more likely to provoke a K-complex or isolated galvanic skin response, than other names, even if the subject failed to respond overtly. Statistical analyses have been made of EEG responses on the basis of ratings of the latter made in ignorance of each particular stimulus. The responsiveness largely, but not entirely, disappears in very deep sleep with high voltage 1 c/sec. waves. The transition from single names to names spoken twice tends to cause arousal.

13. EEG control of the treatment by ACTH of early infantile myoclonic encephalitis with "dysrythmie majeure" (Hypsarhythmia). — H. Gastaut, W. C. Gibson, M. Pitot and M. Vigouroux, Faculté de Médecine, Marseille.

Following the work of Sorel we instituted ACTH treatment in 6 cases of this affection, which is peculiar to young infants, and which was described independently and simultaneously by Gibbs (1952) as "infantile spasms with hypsarhythmia" and by Gastaut as "myoclonic encephalitis in infancy with dysrythmie majeure".

The criteria used in selecting the 6 cases to be presented, were those employed by one of us (H. Gastaut) to describe the illness at "The Colloquium on Infantile Myoclonic Encephalitis" (Marseille, April 1951). These criteria were published in July 1952, in a report with A. Rémond, on the myoclonias, presented before the 18th International Neurological Congress.

In the six cases selected on these criteria, treatment with ACTH has given the following results: (1) the spasms diminished from the first few days of treatment and completely disappeared before the end of therapy; (2) the EEG dysrhythmia, similarly, disappeared before the termination of ACTH therapy; (3) the psychological recovery, on the contrary, always depended upon the chronicity of the illness; the cases treated in the very early stages made a total recovery in this sphere; the cases treated late in the course of their evolution showed no recovery whatever.

Beyond the 6 cases here reported, there has been one further case in which the clinical syndrome has been typical but the EEG picture has not been typical, in that it lacked spike-and-wave forms. Nevertheless the results of ACTH treatment have been good.

In yet another 3 cases, where neither the clinical picture nor the EEG tracings were typical (idiocy with microcephaly, without spasms; bursts of slow spike-and-wave forms, but without delta dysrhythmia) the results of ACTH treatment have been completely negative.

Therefore, the results obtained with ACTH, may be attributed to rigorous electrographic and clinical diagnostic criteria, and above all, to early definitive treatment.

14. EEG study of infantile head injuries. — Mmes Lerique-Koechlin and Teyssonière de Gramont, Hôpital des Enfants Malades, Paris.

Six hundred and eighty-four records were made on 254 children between 2 mos. and 15 yrs., on the whole within 18 days after the head injury. About half the initial records were normal; 50 per cent showed abnormalities: slow waves, sharply localized in the temporo-parietal or occipital regions. They were homolateral in 76, contralateral in 21, and symmetrical in 35 cases.

These children were followed up for a long time — some for 7-9 years. Clinically, in general, they became well quickly; however, in about 10 per cent of cases sequelae were noted: headaches, loss of hearing, hemipareses, and epileptic fits.

The EEG findings enabled us to classify the 132 patients with originally abnormal records as follows: (1) 30 records improved quickly — between 1 and 3 months — even though 16 had fractures and 8 had operations for an extradural haematoma or a serous meningitis; (2) 33 records took from 6-24 months to become normal; 24 of these had fractures, 3 a haematoma, and 1 required decompression for oedema; (3) 56 of the children retained minor abnormalities in the EEG, such as excess theta activity, alpha asymmetry, slowwaves and sharp waves and an excessive susceptibility to overbreathing. Of these, 34 had fractures and 9 had operations; (4) 13 showed specific electrical signs of epilepsy — and only 6 had actual seizures. These children have been followed up for several years. The appearance of spikes and waves, even when epilepsy remained sub-clinical, gave us a chance to give anti-convulsants early.

The clinical development of these cases is on the whole favourable.

The clinical course is more favourable than its EEG counterpart — only 10 per cent of clinical sequelae correspond to 25 per cent of disturbed EEGs. It will be necessary to follow up for a long time those children who retain an abnormal record.

15. Convulsions in the new-born: EEG and clinical aspects. — J. Cadhilac, P. Passouant and M. Ribstein, Cliniques St-Charles, Montpellier, France.

Convulsions in the newborn should be singled out, for some of their aspects are never seen at other periods of life; 90 children have been studied clinically and electrically. All of them had convulsions between birth and the age of one month and a half. An attempt has been made to find out which are the specific electrical and clinical aspects and what are the reasons of their specificity.

(1) *Electrical aspects.* The following points were considered as being characteristic:

The discharges are focal; they start either with slow waves or with rapid spikes; their propagation is restricted either to one hemisphere or to a symmetrical region of the contralateral hemisphere (bilateral frontal for example); not one of the 60 crises recorded was generalized and synchronous, neither initially nor after extension of a focal discharge; the background activity is usually of low voltage and shows short unilateral or bilateral bursts of high voltage sharp waves and spikes; there are two or more different foci in over 50 per cent of the patients.

(2) *Clinical aspects and development.*

Convulsions in the newborn are either only tonic or only clonic; the generalized tonic-clonic pattern of grand-mal type is extremely rare; clonic movements, when they do exist, are localized to a small area, and may involve different territories in succession. They are quite discrete and may remain unnoticed by the family; some crises can correspond to a sob that appears after an electrical discharge of spikes; some crises may consist of apnoea and cyanosis or apnoea and hypotonia; some discharges of less than one minute's duration have no clinical expression at all.

The later development is serious. More than 20 per cent of the patients died and another 20 per cent showed evidence of neuropsychiatric sequelae at the age of one year. The prognosis as to life is related to cerebral damage and to the frequent tendency to status epilepticus. The functional prognosis is also serious: convulsions disappear within a few days and the patient seems to recover at first. A few months later the neurological and mental handicap becomes evident.

The specific aspects of convulsions in the newborn are due to their origin and to the immaturity of the brain.

16. The effect of frequency of stimulation in neuromuscular disease. — J. A. Simpson and J. A. R. Lenman, Northern General Hospital, Edinburgh.

Normal human muscle, supramaximally stimulated, has a summated action potential which decreases regularly in amplitude as stimulation frequency increases above 25-30 per sec. (Wedensky inhibition). It is less well known that the action potential in response to a particular rate of stimulation faster than this is well maintained for several minutes then begins to decrement. We have found that this ''fatigue'' has a slow recovery and that it appears much earlier in muscles innervated by metabolically abnormal neurons e.g. motor neuron disease, polyneuritis and chronic anoxia. Similar fatigability may be shown on voluntary innervation. It is suggested that the production of acetylcholine is deficient, removing a normal ''safety factor''. The same abnormality would explain Hodes' (1948) findings in poliomyelitis without requiring an *ad hoc* peripheral explanation.

The ''fatigue'' closely resembles myasthenic fatigue but the latter shows distinctive features, particularly post-tetanic potentiation of a greater degree. The ''fatigability'' of muscle in chronic hypokalaemia is believed to be different in type but this aspect is being explored.

Fatigability in muscular dystrophy is normal. Certain types of myositis show an unusual increment of muscle response at fast rates to stimulation pre-

ceding excessive fatigability. This is seen also in myasthenic myopathy and resembles the phenomena of slight curarization. This response has occasionally been observed during voluntary contraction of muscle.

17. Some forms of paroxysmal activity seen in corticography, and their relationship to undercut cortex. — M. Fischer-Williams, London Hospital.

In a series of 99 electrocorticograms a "pattern" of periodic activity alternating with relative electrical "flattening" has been observed in 17 cases. These include 9 cases of glioma (astrocycoma and glioblastoma multiforme) 4 cases of metastatic carcinoma (1 multiple and the other 3 probably single tumours) and 2 meningiomas. The "pattern" was seen in tumours involving most parts of the hemispheres (frontal, temporal, parietal and occipital). The paroxysmal discharge usually consists of an irregular mixture of beta and slow activity within the theta and delta ranges. The question arises whether or not this "pattern" in tumour cases is similar in nature to that seen in undercut but otherwise healthy cortex. "Suppression-burst" activity was observed by Henry and Scoville in 1952 from isolated cortex during orbital undercutting, and we have observed similar activity also during orbital undercutting and during hypophysectomy for carcinomatosis, presumed to be without intracranial deposits. The pattern in the tumour cases however differs in certain respects from that seen from the more purely isolated cortex in surgical undercutting, in which the picture is stereotyped. The flattening can be considered as relative and the components in the paroxysmal discharges are on the whole slower with comparatively less beta activity. The characteristic feature shared by the tumour and non-tumour cases is the time relationship: paroxysmal activity ranging from one to three secs. (but varying little in individual cases) alternates with inactivity.

A striking feature noted by Henry and Scoville has been confirmed, namely that with bilateral undercutting the discharge on homologous isolated cortex is not synchronous.

18. Blocking of the occipital alpha rhythm and problem-solving efficiency. — A. Glass, Medical School, Birmingham.

Experiments have been undertaken in an attempt to correlate efficiency in solving arithmetical problems with intensity of blocking of the occipital alpha rhythm. Nine multiplication problems were recorded on tape at two minute intervals and played back to each subject while his EEG was being taken. The point at which each problem was presented and the answer given, was marked on the record at the appropriate time.

The method used to assess intensity of blocking was based on the supposition that since a completely blocked record, or zero change of potential may be represented by a straight line, the ratio between the length of this line (a direct function of the paper-speed) and that of an actual record of the same duration would give a measure of deviation from complete blocking. An index of blocking, calculated by comparing the average rate of change of potential for normal and for blocked records is low in intense, and high in slight blocking.

Records from 10 subjects have been analysed and 90 indices of blocking calculated. Correlation coefficients have been calculated relating blocking indices to: (1) time required for solution, (2) correctness of solution; for different subjects independent of problems and for different problems independent of subjects.

There was a statistically positive correlation ($p. < 001$), between the incorrectness of a solution and the index of blocking, indicating that a mistake is associated with less blocking than a correct solution to the same problem by the same individual. A significantly positive correlation was also found between the number of mistakes made in each problem and the average time taken for its solution.

19. Infantile spasms and hypsarhythmia. — B. D. Bower and P. M. Jeavons, Childrens' Hospital and All Saints Hospital, Birmingham.

The clinical group consists of 22 children with infantile spasms attending the Children's Hospital. The spasms consisted of a sudden, brief, generalized jerk often followed by a cry, the cycle being repeated to form a series of variable number.

The EEG group was obtained by taking all hypsarhythmic records and all records of children with infantile spasms, regardless of their EEG pattern carried out in a four year period at the two hospitals. There were 37 first records. Of these, 32 were those of children under 19 months and only these are further considered. They are compared with the first records of 24 children under 19 months with other forms of epilepsy (not febrile convulsions). All the records were given a score weighted to give maximum marks to those with hypsarhythmic characteristics (utter chaos) and minimum marks to highly organized epileptic records. The scores separated the records into two definite groups. We found:

1. Whereas most of the epileptic group had normal records, only one of the group with spasms had a normal record.

2. Only half of the infantile spasm group had hypsarhythmia, the rest being epileptic (non-hypsarhythmic).

3. There was no correlation between the presence of hypsarhythmia and (*a*) the degree of mental defect or (*b*) the type of spasm (flexor or extensor).

We conclude with Gibbs and Gibbs that the EEG is very useful as an aid to the diagnosis of the syndrome of infantile spasms and mental defect. We find, however, that the first record, although abnormal, has an equal chance of being hypsarhythmic or epileptic (centrencephalic or focal).

20. Diencephalic discharges evoked by penicillin. — T. E. Ogden, National Hospital, London.

The epileptogenic propensities of the antibiotics have been appreciated for a number of years, but it is only recently that antibiotics have been widely used as an experimental tool. Penicillin is the most reliable and effective of these, and when it is injected into the midline diencephalon it causes a bilateral disturbance consisting of slowing of the barbiturate spindles, regularly recurring "penicillin spikes" and eventually paroxysms of fast activity which build up into a generalized electrical and clinical convulsion. Such preparations are ideal for the study of the spread of seizure activity from, and the control of cortical activity by, the diencephalon. Preliminary studies on the distribution and spread of such subcortically-generated activity were presented.

21. The EEG in a patient with obsessional neurosis. — J. G. Gibson and W. A. Kennedy, Maudsley Hospital, London.

The patient was a single 34-year old woman who was admitted to the Maudsley Hospital with an acute and disabling exacerbation of a life-long obsessional disorder. There was no history of epilepsy.

An EEG taken soon after her admission showed irregular discharges of spike and slow waves. Further records confirmed these findings although the amount of abnormal activity showed considerable variation.

Following a hysterectomy for fibroids, the patient developed urinary difficulties and was given potassium citrate. It was noticed that she became more disturbed and an EEG taken during this period showed a marked increase in the paroxysmal discharges. As a result, further records were taken at least weekly for the next five months.

At the end of this period administration of potassium citrate again resulted in the patient becoming more disturbed and the EEG more abnormal.

A longitudinal survey of the EEGs taken during this five-month period showed that the abnormalities correlated with a high carbohydrate diet at the 5 per cent level of significance but that there was no relationship with steroid metabolism or thyroid function.

Four months later, administration of potassium citrate and then after an interval a high carbohydrate diet produced no change in the EEG.

Nevertheless, it is of considerable interest that at the same time when both regimes failed to provoke changes in the EEG they also failed to produce changes in the patient's mental state. Indeed during this period she remained generally co-operative and placid.

22. Verification of the sedation threshold technique. — C. P. Seager, Barrow Hospital, Bristol.

We have repeated Shagass' studies on the "sedation threshold" with some modifications, the most important of which are that we have not utilised slurring of speech as a guide to the sedation threshold, and the period of measurement of fast activity has been of 10 instead of 2 sec. duration. This has been made feasible by means of an electronic integrator.

Two points are considered in the evaluation of the sedation threshold:

(*a*) Whether a valid reading could be obtained from a number of records; 179 measurements were carried out on 130 patients. A value for the sedation threshold was obtained from 168 of these records. Correlation was found between the sedation threshold and the "sleep threshold"; this latter being the minimum amount of barbiturate required to produce a state of sleep.

There was also a correlation between the sedation threshold and the point of disintegration of the alpha rhythm where this had been detectable in the resting record.

(*b*) The correlation between the sedation threshold, diagnosis and clinical assessment of tension.

The range of sedation threshold values of the three diagnostic groups, Psychotic depression, schizophrenia and neurotic depression were found to fall into three ascending series.

Statistical evaluation showed them to be three separate populations.

Clinical assessment of tension did not correlate well with the sedation threshold.

23. Rhythm, anxiety and human "internal inhibition". — Ian Oswald, University of Oxford.

In an initial experiment, a volunteer who had been subjected to very intense, irregular electric shocks, rapidly went to sleep one day when the shocks were less strong than he expected.

Six further volunteers received, in each of several sessions, up to 180 strong electric shocks at regular intervals. Four went to sleep while having the shocks. Habituation to zero of the galvanic skin response, and feelings of derealization occurred.

Thirteen subjects listened for brief tones, at the lower limit of audibility, occurring, with a few omissions, at regular intervals. Intervals used were 10, 5 and 3 sec. There appeared an insistent tendency for sleep to arise over each session as a whole, and for EEG sleep signs to occur between each stimulus, coming and going at, e.g. 3 sec. intervals. EEG arousal with each stimulus — response was sometimes limited to rolandic areas; sometimes indeed to the side contralateral to the hand used for response.

Further experiments were carried out in which, for periods of an hour, subjects moved their arms and legs rhythmically to loud jazz music. Once again EEG sleep signs appeared for long periods, even though movement continued. The quality of the latter became impaired however. Once again fluctuation of EEG signs between those of alertness and sleep, at the rate of movement were seen. Sleep appeared during movement to the loudest and most violent music, but most markedly when a sweet clarinet solo followed. Also when clapping and cheering helped the subject's escape to a dream-world.

These observations must be reconciled with those of Pavlov, with the phenomena of "animal hypnosis", and with certain human responses, such as Sargant has described, of inertia and altered responsiveness subsequent on emotional tension and rhythmic stimulation. It is believed this can be done in terms of contemporary theories, and consideration of the phenomenon of habituation.

24. Studies with implanted electrodes in a case of epilepsy. — R. Cooper, H. J. Crow, D. G. Phillips, W. Grey Walter, W. J. Warren and A. L. Winter, Burden Neurological Institute and Department of Neurological Surgery, Frenchay Hospital, Bristol.

The patient was an intelligent youth of 18 with a history of seizures for 15 years and episodes of agressiveness for 8 years. The seizures could be controlled by drugs but the aggressiveness was intractable. EEGs taken at intervals from 1952 showed various abnormalities in temporal, sphenoidal, frontal and occipital regions, mainly on the left side; all fluctuated from day to day, periods of greater EEG "abnormality" coinciding with a subjective feeling of "brightness". In July 1958, 64 electrodes were implanted in the frontal, temporal and occipital regions of both hemispheres with the technique developed by Bickford and demonstrated to us in Oslo by Sem-Jacobsen and Torkildsen. The electrodes were left in place for three weeks before an operation for left temporal resection and for one week after.

Records were taken regularly with an 8-channel Type T electroencephalograph loaned by Dr. Offner and with a 22-channel Toposcope. Direct coupling was

used in nearly all records and the average-reference system was combined with bipolar connections. The first record, taken two hours after the end of the insertion operation, showed large, widespread, irregularly delta, theta and spike activity in all regions, but this subsided in two days to reveal: (1) an intense focal persistent 3 c/sec. delta rhythm from one electrode in the anterior mid-temporal region on the left side. This was occasionally propagated at low amplitude to the medial temporal and lateral frontal regions. (2) Rhythmic activity at 16-20 c/sec. in the left lateral region spreading up the electrode sheaf with bursts of theta rhythm. (3) Delta waves at 1.5 c/sec. in the left occipital pole, attenuated by opening the eyes. This was replaced by alpha rhythm by the fourth day after the operation. (4) Occasional isolated wave and spike discharges strictly localized to a single electrode in the right medial temporal region, with peak amplitude of one millivolt.

The most striking properties of these features were:

(*a*) Extreme restriction of the 200-600 μV. left temporal delta rhythm and the one mV. right temporal wave and spike discharge to regions of about one centimetre in depth.

(*b*) Propagation with time delays of the temporal delta to physically remote regions.

(*c*) Suppression of the temporal delta during light natural sleep, and its transformation into local paroxysmal polyspikes in deeper induced sleep.

(*d*) Association of temporal spikes with the positive phase of the temporal delta when medication was witheld.

(*e*) Transformation of the focal temporal delta into wave and spike discharges spreading to deep frontal and occipital structures during a spontaneous psychomotor seizure.

(*f*) Replacement of temporal delta by generalized spikes and slow waves during induction of Pentothal anaesthesia.

Recording was continued during and after the left temporal resection. The abnormalities on the left side disappeared and the frequency of occurrence of the wave and spike discharge on the right side was diminished. During the past lobectomy period when alpha rhythms were absent from the left occipital region, 200 microvolt lambda waves were recorded during visual attention from the electrode two centimetres anterior to the occipital pole.

These observations demonstrate some of the mechanisms involved in the constraint and propagation of seizure discharges. They also illustrate the need for detailed study of the physical properties of cerebral tissue.

DEUTSCHE EEG - GESELLSCHAFT

Bad Nauheim, October 7-9, 1958

Secretary: W. GÖTZE
Neurochirurgisch - Neurologische Klinik der Freien Universitat, Berlin

1. **The mechanism of origin of the EEG. — H. Caspers, Munster.**

After a survey of the different bioelectrical basic phenomena of the central nervous system (discharges of neurons, synaptic potentials, evoked potentials, spontaneous macrorhythms) the sources of potentials making up the EEG and their functional and morphological properties are discussed. As demonstrated by numerous investigations with microelectrodes carried out in recent years (Jung, Jasper and others), the neuronal structural elements producing spikes cannot be considered as the sources of the slower potential variations, contrary to the views expressed in the older synchronization theory. The unit activity of the all-or-none type, participates in the formation of macrowaves, at the most only in a secondary way, in the form of a modulator. Newer investigations concerning the properties of the so-called dendritic potentials indicate that the EEG originates from the area of dendrites (Chang, Clare and Bishop; Purpura and Grundfest, and others). As sources of potentials, one has to consider mainly the apical dendrites, the axo-dendritic synapses and the terminal arborizations of unmyelinated terminals. The literature concerning the findings and present problems of research concerned with dendritic potentials which pertain mainly to the question of conduction of excitation and of direct electrical excitability of the dendrites is reviewed, and within this framework personal findings are discussed. They deal with relations between amplitude and polarity of the dendritic potentials and with D.C.-changes at the cortical surface. Moderate positive polarization (anodic polarization) of the cerebral cortex increases the amplitude of the negative dendritic potentials. With increased negative polarization of the cortex obtained with gamma-amino butyric acid local stimulations with high frequency pulses or with cathodal polarization, the polarity of the normal dendritic potential always reverts from negative to positive. With this, there always occur an intermediate stage at which the dendritic response disappears despite a constant intensity of the stimulus. The D.C. level therefore is characterized by a state of balance. In the resting animal this ''indifferent level'' is relatively negative with reference to the ''normal level''. With more pronounced shifts of the cortical D.C. potential, reversals can occur. These findings indicate that the so-called dendritic potentials represent amplitude modulation of the D.C. potential which presumably is produced by the mass of continually excited dendrites in the superficial cortical layers.

After the discussion of the sources of potentials of the EEG, the problem is discussed whether these are capable of authorhythmicity or whether they have to be driven by subcortical impulses. Regardless of how this problem is being resolved it has been demonstrated that the discharging rhythm of EEG generators can be modulated by afferent impulses. For the origin of the ''spontaneous'' alpha-rhythm reverberating processus of excitation between thalamus and cortex

(thalamo-cortico-thalamic reverberating circuits) appear to be of importance (Chang, Morison, Dempsey *et al.*).

Discussion:

Dr. Jung (Freiburg i. Br.):

Dr. Caspers' observations on D.C. potentials after application of GABA seem to me very important. These and O'Leary's and Goldring's recordings of steady and evoked potentials after veratrine suggest that a surface negative D.C. potential shift may give a better explanation of the GABA reversal than Grundfest and Purpura's hypothesis of selective blocking at excitory synapses. This block was not found at the neuronal synaptic membrane.

Curtis and Eccles' multimicroelectrode technique of recording neuronal discharges after electrophoresis of drugs at the synaptic regions has been used by Dr. Grüsser and Saur in my laboratory. It has brought further informations about the direct action of GABA and other substances on cortical neurons: in single neurons of the visual cortex we have found definite neuronal activations by acetylcholine, but no selective block of excitory synapses by GABA.

The steady potential changes of the cortex after thalamic and reticular stimulation, described by Arduini and others, show interesting correlations with neuronal discharges, studied by Creutzfeldt and Akimoto. Thalamo-reticular stimulation increases surface negativity. Therefore, it seems difficult to understand Dr. Caspers' interpretation that reticular stimulation diminished the GABA effect by its D.C. component. Should one not expect the opposite by summation of both surface negative potentials ?

I should like to know more about the "experimentum crucis" of increasing the GABA reversal by cathodic, and restoring it by anodic polarization of the cortex and to hear from Dr. Caspers' about the exact relations between polarization effects and the positive or negative sign of the evoked potential with or without GABA.

Personally I am interested in Dr. Caspers' D.C.-potential findings because they fit with my hypothesis, discussed at the International EEG-Congress 1953: Brain waves may be the result of an oscillating balance between two opposite D.C. potential fields, arranged as dipoles and regulated at a mean level of excitation. If this is right, then we might expect a reversal of surface negative evoked potentials following any surface negative D.C.-shifts, be they of physical, (cathodic polarization) or chemical origin (veratrine, GABA).

H. Caspers (Münster) (*closing*):

(1) Our results agree in principle with those of Arduini and Creutzfeldt. We too found that reticular stimulation produces a negative shift in the surface cortical D.C.-level. A similar change of D.C. components occurs with local cortical stimulation with higher frequency impulses. As stressed by Professor Jung, one would have to expect that the negative shift in the cortex should become potentiated or at least decreased by addition when cortical reticular stimulation are combined. According to our results so far this is however not the case. The D.C.-shift to the negative side is even diminished under these conditions. Similar reversal effects which occur often in the manner of an oscillatory reaction could also be observed with increased cathodal polarization of the cortical surface. With small polarizing voltages, the normal negative dendritic potential is extinguished with higher ones reversed. With a still more marked cathodal polarization however, the primary polarization effect becomes again reversed in the opposite way.

(2) The influence upon dendritic potentials and upon the D.C.-level by GABA was further investigated with electrical polarization experiments. With anodal polarization of the cortical surface the GABA effect is abolished. The positive dendritic potential reverts again to a negative wave. With moderate cathodal polarization on the contrary, the GABA effect is increased. With higher polarization voltages one can again observe reversals of the polarity. The result of this "experimentum crucis" allows in our opinion to conclude that the reversal of dendritic potentials by GABA is a consequence of the D.C. shift. This interpretation is furthermore supported by the observation that cathodal polarization of the cortical surface imitates the GABA effect. With anodal polarization without GABA application the normal negative dendritic potential increases in amplitude.

2. Physical basis of EEG and EEG-recording. — J. F. Tonnies, Freiburg i Br.

After a report about amplifying techniques and recording equipment, the incorrectness of the term "differential" amplifier input was pointed out. It should be reserved for an amplifier reproducing the first derivation of voltage against time ($\frac{dV}{dt}$). Since this direct indication of the steepness of a voltage rise comes more and more into use in experimental laboratories, it is proposed that the balanced input, with rejection of common modulations for a pair of input leads, as invented by the author should be called: "*difference amplifier input*".

The EEG-potentials recorded by macro-electrodes should not be considered as originating from short spikes of cell perikaryons or axons, but much more likely as originating from the great volume and surfaces of the dendritic branches. Following Dr. Caspers' discussion of steady potentials the behavior of dendrites and small interneurons deserves more attention.

The small interneurons, although difficult to record individually, might be very important or even dominant for the total electrical output, by their overwhelming number, and by slower velocities of spread in their extended fibre network. Assuming in dendritic arborizations a slow conduction velocity of the order of 1 m. per sec. an impulse travelling over 5 mm. distance gives a 5 msec. duration. A contribution of such slower processes to EEG potentials, seems more likely than a rhythmic accumulation of 0.6 msec. neuronal spikes.

A new analyser for EEG potentials and for written EEG records is reported. In contrast to previous analysing methods, separating the EEG into several sinusoidal frequency spectra, this new method is entirely aperiodic and makes a statistical evaluation of time intervals between certain points of waves. The live EEG potentials or a previously written record is *scanned on 8 potential levels, and the time intervals between two points of equal level, form the elements of the analysis.* These elements are summed up in 8 classes of different interval length. *After a*

10 sec. period the summations of the 8 classes of interval length are written out on a diagram.

This type of analyser may measure relatively small changes in an individual EEG as effects of various experimental procedures, but a classication of individual EEGs may not give better results than the intelligent inspection of records in daily EEG praxis.

3. Experimental investigations concerning the nature of the spike in the EEG. — A. E. Kornmuller (Goettingen).

Previously the notion was advanced and supported that the spike in the EEG as recorded by mass recording represents the bio-electric manifestation of the action of the satellite cells of ganglion cells and that these satellite cells exert an inhibitory influence upon the ganglion cells (see A. E. Kornmuller).[1] From this it follows that an increased release of the postulated inhibitory substance by the satellite cells has to occur when the spike is most pronounced. Rabbits which were to be used for the manufacture of the inhibitory brain extracts were therefore killed by decapitation immediately after electrically induced convulsive seizures, after these animals had been subjected for three weeks to daily electroshocks. The brains were extracted with acetone and ether and these extracts were dissolved in olive oil to be used for intramuscular injections.

After injections of such extracts into mice, rabbits and monkeys, no motor seizures were observed. Electroencephalographic investigations which were carried out on rabbits, showed that after injections of these extracts, there was an increase in the physiologically present spontaneous spike discharges, and a decrease of the action potentials of striate area in response to an illumination of eyes. These findings are to be interpreted as indicating an increase in threshold.

Monkeys showed after the injection of the extract (60 to 20 mg. per kilogram or more) a definite decrease of motor activity and diminution of excitability (capability to react), which began a few hours after injection and remained for several days. With stronger dosages brief periods of sleep and absence-like episodes occurred without any motor manifestation. In the EEG small bursts of spikes were often observed after injections. The alpha waves and the waves which occurred in conjunction with the spikes faded more and more into the background as the action of the extract increased.

After these experimental investigations the spike will also be considered as a chemical problem. The described extracts are investigated with regard to their therapeutic effect on man. The aneuristic usefulness determines the value of a theory.

4. What conclusions can be drawn from depth recordings and depth stimulations for the regulation of the EEG ? — W. Umbach, Freiburg i. Br.

Three hundred and thirty EEG recordings and bipolar stimulations were carried out in 20 precisely localized points within the basal nuclear and fiber structures of the human brain. These were often carried out together with surface EEG recordings. Twenty-seven records were obtained with electrode assemblies carrying 8 compact points, which were introduced into the basal ganglia. The spontaneous activity showed no wave patterns which were specific for any particular localization within the individual nuclear areas. In each individual case, the recordings showed a good stability of the pattern. Between the depth and the surface of the brain, the most frequent observation besides the well-known phase reversal was that of frequent correlations of frequency and amplitude and only rarely alternating patterns were seen. Single shock and repetitive stimulation (4 to 100 c/sec.) carried out in the depth with different intensities showed unspecific slow projections to the cerebral surface. Latency measurements of the primary wave showed a predominating projection into the anterior cortex. With weak stimuli unilateral responses were recorded whereas with stronger stimuli bilateral responses were observed. Definite conclusions as to the physiological or pathological regulation of the electrical activity of the surface from the depth cannot yet be drawn. However statements concerning the central regulation of vegetative and phychical effects as revealed by depth stimulations can be made.

5. Familial incidence of photo-sensitivity. — D. Schaper.

Fifty four siblings and 26 parents of 57 children suffering from convulsions and showing photo-sensitivity were investigated with identical techniques.

Of the whole group of 137 family members 63 per cent showed photo-sensitivity. Among the siblings this reaction was found in 43 per cent, and among the siblings and parents taken together, in 32 per cent. These findings as well as the repeated demonstrations of photo-sensitivity in two generations point out its hereditary transmission with high penetrance.

6. Concerning the change of EEG foci in epileptics in relation to their attacks. — Hedenström (Anstalt Bethel).

An electroencephalographic phenomenon is discussed, which is observed in many patients during the course of several investigations, and which consists in the fact that the pathological potentials show a shift of their site of predominance from one hemisphere into the other. In symptomatic epileptics in which the side of the cerebral lesion was known, it was found that before the attack the abnormal potentials were most marked on the normal side; whereas after the seizure the focal sign correspond with the clinical findings. The question of whether the cause for the paradoxical asymmetry may be explained by an amplitude reduction preceding the attack, affecting the side of the focus more than the intact side is discussed on the basis of an EEG record taken during the aura of a seizure.

7. Polygraphic observations in *petit mal attacks*. — J. E. Krump and W. Gerardy (Heidelberg).

In 12 juvenile epileptics, the peripheral vegetative changes occurring with petit mal attacks were synchronously recorded with the EEG by taking the oscillogram of the arm, a record of the respiration and of the EKG. In some cases the EMG and the blood pressure were also recorded.

The most frequent change was a diminution of respiration and heart frequency together with a de-

1 Siehe A. E. Kornmuller, zum wesen des EEG auf Grund spezieller Untersuchungen. LV. Internat. Kongr. F. Elektroencephalographie, Brussel, Juli 1957, Pergamon Press, London; Zum Wesen der Epilepsie auf Grund einer Analyse des EEG. Fortschr. Neur. Psychiatr., **26**, 470 (1958); Ein inhibitorisch wirkender Hirn-Extrakt. Arzneimittel-Forschg. (Drug research) **8**, 675 (1959) !

crease of the amplitude and some irregularity in the oscillogram. A hyperpneic reaction with or without tachycardia seemed to occur more frequently with multiple spiking and wave discharges. The same electrographic pattern was sometime seen to be associated in the same person with different vegetative manifestations. The direction and magnitude of the vegetative changes were largely determined by the background level of autonomic activity and by the vegetative stability as was demonstrated by tests carried out with megaphen.

In two tonic convulsions, the first excitory phase of spike activity was accompanied by bradycardia and by a rest of respiration and this was followed during the tonic motor phase by tachycardia and return of respiration. During the post-ictal phase of theta and delta activity, cardiovascular ability could be demonstrated.

A liability of the vegetative apparatus could also be demonstrated in the post-paroxysmal period following spike and wave discharge.

8. Behavior of bio-electrical fields in the case of cerebral tumour. — G. Foitl and H. Petsche, (Vienna).

In a patient with a frontal tumour (dermoid) the phase relationships of the waves were studied with a multivibrator-toposcope. It was shown that the tumor waves also have the character of migrating waves.

The investigations carried out yielded the following results:

(1) The waves propagate primarily along meridians between the inion and the nasion.

(2) They frequently cross the midline where a certain delay of their propagation can be demonstrated.

(3) The distribution of amplitudes shows no constant relationship with the direction of propagation.

(4) The frequency of the waves and their velocity of propagation show a linear relationship within the investigated frequency band of 2 to 10 c/sec.

9. Remarks concerning the technical prerequisites for radioelectroencephalography. — T. Gotze and A. Kofes.

In the beginning the authors discuss the technical prerequisites for radio transmission of bio-electric phenomena. Records of electroencephalograms and electromyograms obtained by this method in healthy individuals and patients with cerebral disease were demonstrated.

Healthy individuals show a diminution and irregularity of the alpha waves when walking. When walking with closed eyes, an off effect can be demonstrated. When walking for a prolonged period of time, with open eyes, sporadic alpha waves can occur again. The diminution of amplitude and the dysrhythmia increase with running. In juvenile patients with convulsive disorders walking produced an increased diminution of frequency and an increase of amplitude until epileptogenic potentials occurred. A delta focus in patients with a tumor showed fading of the slow waves.

Myographic investigations in patients with brain disease are particularly valuable when taken under such a functional load. Minor spastic symptoms such as rigor can be brought out more clearly and degenerative spinal disease can also be more easily diagnosed.

10. Electroencephalographic response of the visual center to photic stimulation. — Laue, Bonn.

In the photo-stimulation device used by the author a xenon high pressure lamp acts as the source of light. Measurements of the light energy are carried out with a radiation thermo-element and a mirror galvanometer. The experimental person looks with one eye into a periscopic ocular. The electrical field of projection of the calcaline sulcus and of the cuneus can optimally be recorded at 2 to 7 cm. above the inion preferably with needle electrodes. When recording with an RC-coupled amplifier, it is sufficient for interpretation that the time scale of 10 ms delivered by an electrical impulse generator corresponds to a 1 mm. displacement of the paper.

The photic stimulus is recorded with a high vacuum photocell. Among twenty experimental subjects investigated by the same method 80 per cent showed the same electroencephalographic response of the visual center. Characteristically, this consists of a diaphasic spike wave with initial negative deflection and only in 40 per cent of the cases this is preceded with an interval of 10 msec. by a small positive deflection of an amplitude of 20 to 30 μV. The peak of the negative wave shows an amplitude of 150 to 200 μV. and the following positive wave one of 110 to 150 μV. In certain cases, there follows an afterphase of spikes. The negative deflection of the spikes begins 64 msec. ($\pm$ 13) after the onset of the light stimulus and the reflex closure of the lids occur only 100 msec. after the stimulus.

The author wishes to contrast this isolated spike potential occurring in response to high energy light flashes of short duration (0.005 sec.) with the sequence of relatively slow waves disclosed by Bartley, Monnier, Laue and Monnier, Cobb and Morton, François-Stefens-Derouck and Ellingson.

PRINTED IN CANADA

THE DUTCH EEG SOCIETY

Academisch Ziekenhuis, Leiden

December 13, 1958

Secretary: O. MAGNUS
St. Ursulakliniek, Wassenaar, Holland

1. The relationships between electroencephalographic and psychological data in normal adults. — P. F. Werre, J. W. N. De Lange and W. Storm Van Leeuwen, Leiden.

This investigation (see also Werre 1957) pertains to the association of data obtained by elaborate EEG and psychological examinations of 24 normal adult subjects. The psychological data were obtained by means of the Rorschach, Four Picture and Wiggly Blocks tests and by an interview.

The subjects could be grouped in the following ways. By assessing of each subject the number of delta and beta waves in a sample of 100 waves in the temporo-occipital region, all subjects could be plotted into a diagram. The number of delta waves was plotted on the vertical axis, the number of beta waves on the horizontal axis. In this way groups of subjects were found with more or less indentical psychological characteristics and with similar EEG properties. Subjects having, among other things, a high amount of alpha waves, no or some delta waves and no or few beta waves are psychologically characterized by extensivity, i.e. durability, after-effect, profoundness, etc. of feelings and strivings. Subjects having, among other things, relatively many beta waves are psychologically characterized by intensivity, i.e., vehemence, mobility, velocity, etc. of feelings and strivings.

Tentatively is concluded that there are no unique associations between any single EEG variable and any specific psychological parameter, whereas the coordinate representative of EEG and psychological attributes strongly suggests that certain EEG patterns are contingent upon a definite measurable psychological grouping.

2. The cortical response to photic stimulation. — M. W. Van Hof, Leiden.

The cortical response to photic stimulation in human subjects was investigated by means of a graphical averaging technique.

The flashing frequency varied from 3 to 11 per sec. Ordinate values (time intervals 2.7 msec.) with regard to an arbitary zero line were determined.

The average values of the corresponding ordinates of 40 flashing periods were calculated.

In general the pattern thus obtained was similar to that described by Monnier (1952). At flashing frequencies higher than 3 per sec. the first negative wave (c wave, latency about 90 msec.) was followed by a second negative wave (latency about 110 msec.). At higher flashing frequencies there was an interaction of the overlapping responses.

At present an investigation of the photic response in psychiatric patients is in progress.

3. The so-called: "Frequency specific conditioned response". — W. Storm van Leeuwen, Leiden.

In cats electrical responses of various cortical and subcortical regions to combinations of acoustic and rhythmic photic stimuli have been recorded and analysed. Conditioned responses are obtained in various regions. In a patient activity at 11-13 sec. in the motor area is enhanced during conditioning procedures. It is suggested that the conditioned responses in the cat experiments as well as in the patient are caused by enhancement of previous existing rhythmic activity. This enhancement indicates inhibition of the structures involved.

THE WESTERN SOCIETY OF ELECTROENCEPHALOGRAPHY

Carmel, California, February 25-27, 1959

Secretary: Dr. KENNETH BLINN
4120 Atlantic Ave., Long Beach 7, California

1. The use of the electroencephalogram in pediatric practice. — Elizabeth Lodge Rees, Castro Valley, California.

The need for thorough study of children with severe behavior problems is stressed. All too frequently, especially in schools, juvenile halls, and the Youth Authority psychiatric diagnoses are made without complete neurological evaluation including electroencephalography. Brain damaged children and their parents may be treated for years by ancillary personnel in the psychiatric field.

Sometimes the electroencephalogram can be used in treatment. Material evidence supporting diagnosis can be very impressive. It is very important that the physician realize exactly why he is doing this and the limitations of the EEG. Similar use may be made of EEGs in prognosis. Consultations with various agencies handling the child can be facilitated by proper use of EEG reports.

2. Genetic patterns in epilepsy as recorded by the electroencephalogram (A two-family study). — Edward E. Shev and Charles L. Yeager, San Francisco, Calif.

Our paper presents a study of two families which shows the close relationship between heredity and epilepsy. One of the families consists of the parents and four children. Two of these children are identical

twins, who have epilepsy. An electroencephalographic study of the parents and the other two children uncovered abnormal electroencephalographic (brain waves) patterns for the mother, brother and sister. The father's test was normal. In the second family, the mother was normal but her first husband had an abnormal test and a history of epilepsy in his family background. Their two children had abnormal electroencephalograms and one of these children had clinical epilepsy. The mother's second husband's study was normal and the two children of this marriage showed no evidence of abnormality by electroencephalographic or other studies.

This unique family study further illustrates the importance role of genetics in epilepsy.

3. The electroencephalogram in silent brain tumors. — J. Sloan Berryman, Los Angeles, Calif.

The electroencephalogram may be of great value in early recognition of relatively superficial tumors in areas of the brain which are inclined to be silent until large lesions develop. A case history was reported of a 45 year old man who had a four month history of left homonymous hemianoptic field defects of very brief duration. He did not come to the attention of a neurologist until he had a grand mal convulsion at work with no residuals following the convulsion. Neurological examination at that time was entirely normal, including perimeter and tangent screen studies of the visual fields. Electroencephalogram at this time, however, showed a distinct delta focus in the right occipital lobe and isotope uptake studies revealed a concentration of increased radiation in the region of the right and left occipital lobes. Patient subsequently had surgery at which time a glioblastoma was removed from the area of the right occipital lobe. Patient did well for a year following which the tumor recurred and he eventually succumbed. In this case the electroencephalogram was the first objective finding of localized brain damage and was supported by isotope study and the earliest symptoms.

4. Experiences in the use of tilt table in electroencephalograms. — Warren E. Porter, San Francisco, Calif.

A tilt table was constructed with extremely minor variations from that used by Dr. John Meyer *et al.*, in their tilt table studies for cerebrovascular insufficiency that they reported in 1956. We chose 29 ambulatory patients who presented various symptoms of possible early ischemic disease, of mainly the posterior circulation, such as increasing episodes of vertigo, transient visual changes, transitory — and sometimes permanent — neurologic residuals of hemiparesis and/or hemisensory abnormalities. A total of 34 separate runs was accomplished, and a total of 38 tilts was made. The patients were tilted to 70° (over a period of 5 to 7 sec.) for an average period of 2 min. Their blood pressure fall was very often unremarkable; sometimes the pressure was increased. In no instance did we pick up any abnormality that would suggest cerebral ischemia. At no time did we add carotid compression to the test. Our purpose was to see if we could use tilting, a relatively natural procedure, as a useful routine part of our studies in the older age group with or without cerebrovascular disease, to anticipate impending cerebral infarction. In our hands, the test as run has little applicability to a routine ambulatory elderly population ranging in age from 40 to 80. We intend to explore more chronically invalided, bedridden patients.

5. Preliminary study of stimulation and recording in globus pallidus and thalamus in man. — Richard D. Walter, Robert Rand and Ross Adey, Los Angeles, Calif.

During operative procedures for the relief of paralysis agitans stimulations studies and recordings have been undertaken from the globus pallidus and the nucleus ventralis lateralis of the thalamus. Electrical stimulation in the nucleus ventralis lateralis (as radiologically determined) at rates between 1 and 5 per sec. frequently evoked recruiting responses as reflected in the scalp recordings. This was most marked in the fronto-central leads and to a lesser degree in the central-parietal leads of the same hemisphere. In two cases, depth records showed a rapid, rhythmic "spindling" activity at 12-16/sec., in one case in the thalamus and in the other the globus pallidus, while the patient was lying quietly. The spindling was abolished during both spontaneously and electrically induced tremor. In one of these cases, stimulation of the thalamus at 5/sec. was effective in inducing a generalized 5/sec. cortical rhythm with an episode of induced tremor lasting beyond the period of stimulation and subsiding as the induced cortical rhythm waned.

6. Positive activity as the earliest evidence of drowsiness in routine EEG tracings. — Warren E. Porter, San Francisco, Calif.

Over the last five years in our search for 6-14 per sec. positive activity, it has become evident that there is a great deal of semi-positive or transitory positive, almost spike, activity that appears in a large percentage of our awake records. We have reviewed specifically segments of our electroencephalographic records for the last year at Letterman Army Hospital, and we find that in our records where we attempted to get the patient to sleep, this is found more commonly. In our patients who are extremely drowsy at the onset of the EEG, this activity is even found sometimes during hyperventilation. This finding is present on the average of 76 per cent of the time. It has several interesting characteristics: it is extremely brief in duration, usually being of no more than one second's duration. Also, it occurs in any lead, preferring the fronto-occipital. Thirdly, it precedes other evidences of drowsiness, such as reduced alpha activity, by at least 10 to 20 sec. The activity is much less distinct and often a mixture of slower and faster rates. We have found this a useful guide to alert us to the degree of drowsiness in the patient.

Historically, early Gibbs reported 6 and 14 per sec. waves as normal variations in sleep. Later, they relegated this finding for the most part to seizure (thalamic) disorder. The activity reported here is not to be confused with these findings; this activity *precedes* sleep and heralds it.

7. Technical problems encountered in electroencephalography with altitude chamber experiments. — George N. Thompson, Reuben Strauss, C. I. Barron and Morris Cohen, Burbank, Calif.

This paper is a preliminary report of experiments now in progress, of the electroencephalographic phases

of physiological and neurological research with white rabbits in altitude chamber experiments. It is less a presentation of results than it is a discussion of the technical problems that have been encountered, some of which were severe. Since others may be doing similar work, it is hoped that our problems and the efforts that we have exerted to solve these may assist others to avoid duplication of effort.

To date we have used the altitude chamber to decompress rabbits to a maximum altitude of 40,000 feet at a controlled rate of ascent, length of time at altitude, and controlled rate of descent. Variables measured during the experiments were electroencephalographic changes, electrocardiographic changes, arterial oxygen saturation, blood pressure, heart rate, animal temperature, respiratory rate, chamber temperature and chamber ventilation.

The purpose of this research is to determine the effects of high altitude upon animals. Most of the technical problems that we have encountered have been those of the electroencephalograph, and have to do with electrical interference of one type or another. We have concluded that every electrical connection and instrument must be shielded completely. Problems of grounding, power sources and effects of altitude upon electronic instruments are discussed.

The final phase of the project will be an attempt to correlate physiological changes with submicroscopic brain changes due to the stresses placed upon the test animals.

8. **Conditioning of a photically-driven cortical response. — N. A. Bercel, Edgar L. Lowell and William F. Dossett, Los Angeles, Calif.**

This experiment constituted an exploration of the modification of the occipital rhythm by means of classical conditioning.

Sixteen, experimentally naive, adult subjects were used. Each subject, seated in a semi-darkened room, was presented, at randomly-spaced time intervals, with a series of 1000 cycle, supraliminal tones. The duration for each tone was generally 10 sec., and after a 4 sec. delay, was followed by 6 sec. of intermittent photic stimulation of a frequency at or near the subject's alpha rhythm. The photic stimulus (UCS) was paired with the tone (CS) on approximately 75 per cent of the trials.

Changes in the rhythmic activity recorded from the right occipital region were analyzed. The activity occurring during the 4 sec. delay intervals (CS-UCS interval) was found to change as a function of the number of conditioning trials. The frequency of the rhythmic activity in this 4 sec. anticipatory period became more and more specific to the frequency of the photic stimulus. The curve of acquisition for this anticipatory synchronous response was linear over the first 21 trials. No such trend was found for the activity occurring in the 4 sec. interval *preceding* the onset of the tone. This interval was used to establish a base level for the EEG changes over time which could be employed as a control for adaptation for each subject. The reliability of the acquisition trend was confirmed by a detailed test of statistical significance.

Although this experiment did not provide for pseudo-conditioning controls, it nevertheless shows that systematic changes in EEG response can be produced by the experimental procedures used in this study, and that these changes afford evidence for the establishment of a conditioned driving response in the occipital cortex of humans.

9. **Ion movements in cerebral cortex. — J. P. Schadé and A. Van Harreveld, Pasadena, Calif.**

A histochemical method for the detection of chloride ions in the cerebral cortex has been developed. The method was used to visualize the position of chloride ions under various experimental conditions. A comparison was made between the chloride distribution in (*a*) normal oxygenated cortex, (*b*) in cortex a few minutes after circulatory arrest, (*c*) during spreading depression and (*d*) during convulsive electrical activity.

(*a*) In control cortices chloride is rather evenly distributed. It is mainly present around apical dendrites and in the space between the apical dendrites.

(*b*) In asphyxiated cortices the chloride is mainly inside the apical dendrites. In the parikarya a smaller increase in chloride content is observed, no increase in chloride ions could be found in the axons and the smaller dendrites.

(*c*) During spreading depression a similar but less pronounced transport of chloride occurred into the apical dendrites.

(*d*) An even smaller increase in chloride ions in the apical dendrites was found during convulsive patterns. The observed chloride movements strenghten the postulate that during various experimental conditions sodium-chloride moves from intracellular spaces into neuronal elements of the cerebral cortex.

The apical dendrites in normal cortex contained more chloride than those of nembutalized cortex. It is postulated that even the excitatory processes which give rise to the normal EEG thus seem to result in a sodium-chloride influx. While sodium-chloride moves into the apical dendrites during the normal and even more during convulsive activity of the cortex the mechanism removing the electrolytes can be expected to be active. What we observe then is a steady state condition which is characterized by a certain chloride content of the apical dendrites, determined by the inflow and removal of sodium-chloride.

10. **Bilateral synchrony and arousal in EEG of fish. — J. P. Schadé, Pasadena, Calif.**

Bipolar surface electrodes were used to record electrical potentials from the brain of the goldfish, the trench and the dogfish. Characteristic patterns of EEG were described for telencephalon, mesencephalon, cerebellum and medulla oblongata. Changes in these patterns under deepening urethane narcosis were noted.

Rapid repetitive flashing light caused a change in the normal EEG of the midbrain which resembled the mammalian arousal. High frequency (18-24 c/sec.) low amplitude activity replaced the characteristic low-frequency waves (7-14 c/sec.). Monocular blinding abolished the response to single light flashes, in the contralateral half of the tectum opticum; the arousal and bilateral synchrony remained, however. Even after cutting the commissures between the left and the right tectum opticum these phenomena remained the same as before. Only after cutting the thalamic nuclei in the medial plane the bilateral synchrony and the arousal reactions in the midbrain disappeared.

The originator of both phenomena is probably located in a nucleus in the thalamus.

Regional differences in the tectal response to single light flashes were described. Microelectrodes were used to record the photic response from deeper tectal layers. After destruction of part of the retina by electrocautery a disappearance of a part of the photic response was observed in restricted tectal areas. The distribution of the areas of changed response was shown to correspond to a coarse overlapping projection of retinal quadrants of the fish eye, onto the contralateral optic tectum. A possible basis for the localization of this projection, in agreement with anatomical and electrophysiological findings, was described.

11. Some observations on the neuronic shutter. — Enoch Callaway III and John D. Alexander, Jr., San Francisco, Calif.

The alpha rhythm probably reflects an excitability cycle of some sort. This paper reports a new phenomenon which would support the notion of a ''neuronic shutter'' operating at about 10 c/sec., and which also suggests that this ''neuronic shutter'' is driven by stimuli.

Regular trains of sensory impulses were presented to subjects who were instructed to respond when they observed cessation of the stimuli. Reaction times to the termination of these impulse trains were measured. Relationships between reaction times and impulse frequencies were plotted and non-linear perturbations in reaction time were observed at stimulus frequencies near ten cycles per second.

12. Relative times of occurrence of alpha waves recorded from electrodes arranged linearly from frontal to occipital regions. — Bill Garoutte, Stanley Goodman and Beverly Timmons, San Francisco, Calif.

Normal alpha activity was recorded from series of 4 to 8 scalp electrodes arranged sagitally or parasagitally from occipital to frontal regions in 20 human subjects.

There was, in every case, a difference in time of occurrence of waves in the A-P (or P-A) direction when recording parasagittally 2 cm. from the midline. The occipital wave or the frontal wave occurred earliest about equally often. The differences in time of occurrence averaged 30 to 40 msec., whether from front to back or back to front. There was much variation from individual to individual, and within a given individual from time to time. Generally, brief series of waves occurring earlier in the occipital region alternated with brief series occurring earlier in the frontal region. In some individuals, the waves appeared earlier in one or the other region consistently.

When recording along the midsagittal line, the waves tended to appear simultaneously in all areas from front to back. Recording from right and left sides simultaneously revealed bilaterally similar A-P time differences. These two findings taken together suggest that the A-P time characteristics found on midline recording may result from the electrical averaging of bilaterally synchronous activity.

The significance of these data in relation to the ''pacemaker'' concept will be discussed.

13. Rhythmic relationships between waves recorded from linearly arranged cortical electrodes in the cat. — T. H. Tjiook, Bill Garoutte, Robert B. Aird, Milton Delucchi and John Garcia, San Francisco, Calif.

Scalp and cortical EEGs were obtained, using an eight-channel Offner EEG apparatus operated at a paper speed of 15 cm. per sec., from 8 cats lightly anesthetized with Nembutal or ether. The scalp records were taken from 8 occipito-frontally oriented electrodes lying over the line of the suprasylvian gyrus. Following the scalp recording, the cortex was exposed surgically. Records were then taken from 8 cortical electrodes directly under the sites of the corresponding scalp electrodes, as determined stereotactically.

The resultant records were analyzed (1) as to number of waves in the different cortical positions which appeared simultaneously at any given instant, and (2) as to the millisecond differences in times of occurrence between these same waves from the various positions. The following observations were made.

Waves recorded from the various occipito-frontal positions tended to occur synchronously in both the scalp and cortical studies. The time differential between frontal and occipital waves rarely exceeded 10 msec. These observations were quantitatively but not qualitatively different from those which have been made in the human.

On scalp recording, the number of electrode positions showing waves occurring simultaneously was greater under Nembutal than under ether anesthesia. Synchrony as so defined diminished from scalp studies to cortical studies. A cortical lesion caused the synchrony in ether studies to increase to the same level as in the Nembutal studies. The difference in effect of Nembutal and ether on the synchrony of cortical waves will be discussed in relation to the primary sites of action of the two drugs, combined with the shock effect of the cortical lesions.

The permanent address of the Western Society of Electroencephalograph Technicians is P.O. Box 5276, Phoenix, Arizona. Any and all information regarding the Society may be obtained at this address.

EASTERN ASSOCIATION OF ELECTROENCEPHALOGRAPHERS

Winter Meeting, Ste Marguerite, P.Q.

February 27-28, 1959

Secretary : Dr. JOHN W. SCOTT
Toronto General Hospital, Toronto, Ont., Canada

1. **A case of diminishing EEG abnormality in an expanding lesion. — DANIEL SILVERMAN and MATTHEW T. MOORE, University of Pennsylvania, Philadelphia, Pa.**

One of the neurologic problems that electroencephalographers are called on to help the clinician with is the differentiation between an expanding intracranial lesion and a vascular thrombosis. Diminishing focal EEG abnormality usually is accepted in this differential problem as a reliable indication of a resolving thrombosis. This EEG phenomenon was recently observed in a 50 year old man. Ten days before the initial examination he noted inability to see to the left and a slight headache. The EEG revealed a right occipital delta focus with some bilateral spread. He was hospitalized, experienced more headache, and five days later spinal puncture revealed increased C.S.F. pressure and proteins; the second EEG showed a diminished theta focus. At operation a right occipital metastatic bronchogenic carcinoma was removed. The Graduate Hospital records of expanding lesions where serial EEG studies had been done and the literature on the subject were reviewed. Various mechanisms for this phenomenon were discussed: hemorrhage within a tumor, suppressive effect of medication, foreign body type of reaction from a metastatic tumor and shifts in intracranial pressure. In the case presented, the mechanism believed to be responsible for the change was a transient reduction of intracranial pressure and local edema due to the spinal puncture several hours before the EEG.

2. **Distribution of slow activity induced by hyperventilation. — HAROLD H. GOLDBERG and HANS STRAUSS, Mount Sinai Hospital, New York, N. Y.**

The patterns of slow wave onset and distribution during hyperventilation in 233 electroencephalographic records having an adequate response to hyperventilation were analyzed. Electroencephalographic leads during the 2 to 3 min. period of hyperventilation consisted of the following pairs: frontal-central; parietal-occipital; posterior temporal-ear lobe; mid temporal-anterior temporal.

The following observations were described:

(1) With increasing age there is a definite shift of slow activity induced by hyperventilation from the occipital regions to more anterior regions. The greatest change occurs during adolescence.

(2) The region containing the largest amount, the highest voltages and the slowest activity conformed to the region where this slow activity first appeared.

(3) In the older age groups a reverse pattern of slowing, i.e. parietal-occipital slow activity instead of frontal-central, was found more often in patients with abnormal resting records. This pattern was not, however, found in all patients with abnormal resting records.

(4) A correlation between the clinical diagnosis and the distribution of slow activity induced by hyperventilation was present insofar as reversed patterns of slowing occurred more often in patients with a convulsive disorder than in others. In addition, if the slow activity began as a diffuse and symmetrical burst there was a high correlation with the clinical diagnosis of a convulsive disorder.

3. **Recurrent inhibition. — V. B. BROOKS, Rockefeller Institute, New York, N. Y.**

Repetitive antidromic volleys in the cat's pyramidal tract inhibit discharges of pyramidal cells evoked by electrical stimulation of ipsilateral cortex or of the contralateral foot. The animals were either lightly anesthetized with barbiturate anesthetics, or were locally anesthetized, and immobilized with neuromuscular blocking drugs. Pyramidal cells were identified by responses of constant, short latencies, and by their ability to follow antidromic stimulation at frequencies over 200/sec. The conditioned cessation of activity does not involve refractoriness because the conditioning volleys need not discharge the test cell. The inhibition begins approximately 5 msec. after the end of conditioning stimulation, reaches maximum at about 20 msec., and wanes to zero between 30 and 40 msec. The results suggest that the inhibition is mediated by recurrent axon collaterals of pyramidal cells. This phenomenon will be compared with spinal recurrent inhibition, and with similar effects on afferent pathways. The suggestion is made that the inhibition of adjacent cells is a general property of neurones in projection systems, and that it can be instrumental in the production of contrast and in the maintenance of stability.

4. **Studies on the supracallosal mesial cortex of unanesthetized, conscious cats. — JOHN R. HUGHES and JOHN A. MAZUROWSKI, Meyer Hospital and Buffalo Medical School, N. Y.**

The supracallosal mesial cortex of conscious, unanesthetized cats was studied with the use of implanted electrodes. The mesial surface was mapped for movement with the use of a bidirectional ''noninjurious'' waveform. Two ''feluncuii'' are found: the anterior one has a lower threshold than the posterior one. The face is represented at the anterior and posterior portions of the mesial region with the extremities in the middle. The majority of all observed responses involve movements of the face and head. Ipsilateral and bilateral responses are prominently represented on the posterior feluncuius. Evidence is noted to suggest that functions of the entire supracallosal mesial cortex of the cat may include a motor representation. Recording studies show that full-blown electrographic seizures of the limbic area feature high amplitude spike and wavelike complexes, not usually seen on the lateral surface, but spreading to the hippocampus. These seizures clinically featuring bizarre behavior patterns and autonomic dysfunction, are psychomotor-like in character. Photic driving can be seen throughout the entire

mesial surface. Responses resembling the K-complex in man are seen well on the mesial surface. The area on the mesial surface showing the maximal amplitude of the K-complex is the anterior limbic area where sleep spindles of 12/sec. are also maximally represented.

5. Brain histology after repeated cerebral stimulation. — José M. R. Delgado and A. P. Rodríguez Pérez, Yale University School of Medicine and Cajal Institute, Madrid, Spain.

Histological study has been made of 50 needle tracks and adjacent areas in the brain of 20 monkeys in which electrode assemblies had been implanted for periods of 68 days to 4 years and 2 months. During this time electrical stimulations had been applied a few times to some points and thousands of times to others. The usual parameters employed were square waves, 100 c/sec., 0.2-0.5 msec. pulse duration, 0.1-3 mA., with a limit of 10 mA. The brains were embedded in paraffin, sectioned at 10 μ, and stained by the Klüver, Spielmeyer, Nissl, or silver technique. The following were studied: maximum and median diameter of the track, capsule, uniformity, foreign body granuloma, unspecific infiltration, proliferating capillaries, hemorrhage, necrotic tissue, edema, neuroglia, myelin, and neurones. Reaction was greater in myelinated fibers than in neuronal fields. Extracapsular infiltrative reaction with collagen tissue, macrophages, and nests of giant neuroglia cells was observed in one case. Electrical stimulation produced no detectable histological change with either uni- or bidirectional pulses. Local excitability and EEG activity will be discussed in relation to the histological findings.

6. A survey of EEG's on 1300 RCAF new entry aircrew. — H. P. Brent, J. R. Smiley and T. J. Powell, RCAF Institute of Aviation Medicine, Toronto, Canada.

Approximately 1,300 EEG's taken on RCAF new entry pilot candidates between January 1955 and June 1958, were interpreted independently by two electroencephalographers. The EEG's were classified into six categories ranging from "normal" to "unacceptable" and a separate classification was also made on the basis of EEG changes during hyperventilation. A comparison of EEG ratings by the two electroencephalographers, on the Six-Category Scale, showed full agreement in 78.2 per cent of cases. There was a one-point difference in 17.3 per cent of cases, a 2-point difference in 3.4 per cent of cases, and a 3-point difference in 1.1 per cent of cases. Comparison of the students' Pass-Fail records in Flying School with their EEG ratings by each of the two electroencephalographers, showed no association between success in flying training and EEG rating. Similarly, no association was found between EEG changes during hyperventilation and the students' Pass-Fail record. Figures on fatal flying accidents in the group under study are too small at present to show significant differences for the various EEG classifications. It is concluded that there may be considerable divergence of opinion in the interpretation of the same EEG by two electroencephalographers; and that the EEG has not yet proven of value in predicting success in flying training.

7. Changes in EEG in response to physical stress. — C. W. Sem-Jacobsen, Oslo, Norway.

A jet fighter pilot is subjected to considerable physical as well as mental stress during rough flight. This stress can in some instances render a pilot unconscious. After preliminary studies it was possible to make EEG recordings during rough flight in a T-33 jet aircraft. Recordings were made from before take-off till after landing, thus including recording at rest before and after flight.

A group of pilots were tested during a standard flight. The majority of pilots showed only minimal changes in their record. One third of the pilots had marked changes of 2-8 sec. duration in their record, and a few showed prolonged major changes.

By comparing the pilots' EEG record with the military record of their flight ability a high correlation was found. Thus, the good pilots showed only minor changes in their airborne tracings. The major changes in some records seem to explain these men's tendency to pilot errors.

Results obtained indicate airborne EEG recording as a promising method for the study of the combined flights stress as well as a method for the selection of pilots.

8. Clinical and EEG studies during the carotid amytal test for cerebral dominance. — T. Rasmussen and M. House, Montreal Neurological Institute, Montreal.

We have now carried out Wada's carotid amytal tests for determination of cerebral speech dominance in 50 patients, in whom there was uncertainty as to the lateralization of speech dominance, and in whom craniotomy was planned. In most patients the test has been carried out bilaterally. The production of a temporary hemiplegia contralateral to the side of the intracarotid injection of 200 mg. of 10 per cent sodium amytal with preservation of speech provides identification of the non-dominant cerebral hemisphere as regards speech representation. The production of aphasia during the temporary hemiplegia identifies the cerebral hemisphere injected as containing the representation of speech. The use of this test has permitted more radical cerebral surgery in left handed and ambidextrous patients with safety as regards speech functions. The data concerning the lateralization of speech representation in these 50 patients will be summarized. Samples of the EEG records that have been made during some of these tests will be shown.

9. On the development of 6 and 14 per sec. spikes. — David R. Metcalf, University of Colorado School of Medicine, Denver, Colorado.

As part of a longitudinal study of human growth and development, serial electroencephalograms have been obtained on a group of children starting at age 3 weeks. Among 40 subjects, 6 and 14 per sec. spikes were found in one individual, an expremature with no neurological disturbance.

Sixteen electroencephalograms (14 asleep) have been obtained on this child (2 months to 7 years). Six and 14 per sec. spikes were first noted at age 4 years 6 months and have been seen with varying clarity on all 8 successive tracings. With a few minor exceptions, there are no other questionable findings in this individual's EEG series.

As noted by others, the qualitative nature of the discharges varies with recording technique and depth of sleep. It is likely but undemonstrated that other factors such as physical and physiological developmental variables may influence the appearance and quality of these discharges. The gradual development of the discharges is traced from the first minimal

findings through a period of great frequency and clarity of spiking to the present decreased quality and quantity of spiking. Pertinent clinical information will be presented and discussed with regard to possible relations to the EEG findings.

10. Gross figures. — JOHN A. ABBOTT, Massachusetts General Hospital, Boston, Mass.

In a number of abnormal states the EEG has the following characteristics: synchronous waves occur at 2 sets of electrodes over different regions of the scalp (e.g. over the right anterior and left posterior regions); these waves, though synchronous, are of opposite polarities with respect to a common remote electrode; between the regions sampled by these two sets of electrodes there is a strip where these waves are not apparent when electrodes in this strip are linked to the common remote electrode; such regions may, from time to time, vary in extent and location. "Gross figure" is used to designate a distribution of potentials which gives these characteristics to the EEG. Gross figures and their associated abnormalities (including notably metabolic disorders) are contrasted with the voltage distributions associated with epilepsy, sleep and lesions causing the more familiar foci of slow waves which are synchronous and of the same polarity with respect to a common remote electrode.

11. Resetting of cortical neuronal rhythms. — ROGER M. MORRELL, The Montreal Neurological Institute, Montreal.

The rhythm of repetitively firing cortical neurones in the dog's cruciate gyrus can be reset by antidromic (pyramidal), orthodromic, or direct (axonal) impulses interjected into the natural train. Orthodromic impulses were delivered by cortical stimulation or thalamic (VL) stimulation. Direct stimulation was accomplished by impaling a single corticospinal fiber in the pyramid, or a neurone soma which responded to pyramidal stimulation. The response was recorded with a bridge circuit through the same microelectrode used for stimulation.

Cortical neurone rhythms could not be reset by direct (intracellular) stimulation, although antidromic, orthodromic and direct (corticospinal axon) interjected impulses reset the rhythm. This suggests that the intracellular stimulus did not invade the structure responsible for the rhythm, and that random synaptic bombardment is probably as important as authorhythmicity in determining the cell's pattern of firing. Since antidromic and direct (axonal) impulses reset the rhythm, recurrent collaterals probably play a role.

Increased hyperpolarization following stimuli interjected into high frequency bursts strongly indicated the presence of cumulative inhibitory feedback, again over recurrent collaterals. Antidromic impulses did not reset strychnine rhythms. Since strychnine blocks the inhibitory endings of Renshaw cells in the cord, this might suggest that resetting of normal cortical rhythms takes place via recurrent collaterals and inhibitory interneurones.

12. Brain stem propagated after-discharges from the amygdala.[1] — O. J. ANDY and J. MUKAWA, University of Mississippi Medical Center, Jackson, Miss.

The pattern of the propagated amygdaloid after-discharge to the rostral mesencephalic and caudal diencephalic brain stem was studied in 30 awake cats.

Electrodes were placed in the amygdaloid nuclei and in the mesencephalic and diencephalic brain stem structures. After-discharges were electrically induced in the amygdala with a Grass stimulator and recordings made on a Grass 16 channel electroencephalograph. Two hundred and twenty eight histologically verified points in the brain stem were studied. Three hundred and eighteen discharges were analyzed with respect to amplitude and laterality. The findings were plotted on frontal planes according to the Atlas of Jasper and Ajmone-Marsan.

Propagated amygdaloid discharges appeared to be most concentrated in the areas of the hypothalamus, the habenula, the habenular interpeduncular tract and the interpeduncular nucleus. The next greatest area of propagation was to the ventral and lateral mesencephalic reticular region. Propagation appears to be predominantly ipsilateral throughout the entire brain stem. Contralateral propagation acquires its greatest amplitude in the areas of the habenular nuclei and hypothalamus.

These results suggest two major pathways for propagated amygdaloid impulses to the brain stem, a dorsal and ventral. The first, through the habenular system and, second, through the hypothalamus. The implication of these systems undoubtedly accounts for the peculiar behavioral changes during varied forms of psychomotor seizures.

13. Experiments on localization of genital function in the brain. — PAUL D. MACLEAN, BRYAN W. ROBINSON and DETLEV W. PLOOG, National Institute of Mental Health, Bethesda, Md.

There is evidence that a neural system involving parts of the hippocampus, cingulate gyrus and septum is implicated in pleasure and grooming reactions and sexual manifestations, including penile erection (MacLean, 1954; 1957).

The present study deals with further experiments on localization of genital function in the brain. A progress report is given of experiments on squirrel monkeys in which we have employed a wide variety of parameters of electrical stimulation and have used penile erection as the end-point. One very effective locus lies in the medial preoptic region rostroventral to the anterior commissure where fibers course to and from the septum.

Approximately between levels A10-A6, we have encountered two different types of nervous elements whose stimulation results in erection. One responds optimally to stimuli at 20-30 per sec. and pulses of 1.5 msec.; the other to stimuli at 90-110 per sec. and pulses of 0.1 msec. Evidence is presented that allows one to infer that the elements of the former lie rostral to and possibly synapse with the latter, and that simultaneous stimulation of both results in summation. The latencies of penile erection in each case are respectively 6-7 sec. and 3 sec. Stimulation of the slowly responding elements is frequently followed by propagated afterdischarges recorded from electrodes in the region of the hippocampus.

14. Sensory interaction in the cerebellum of anesthetized cats. — W. P. KOELLA and J. D. LOESER, Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

Cats were anesthetized with chloralose. Loudspeaker clicks, short light flashes, and short electrical

[1] Aided in part by a grant from the U.S.P.H. Grant Number 5104-B.

shocks to the skin (referred to as ''tactile'' stimuli) were used to induce sensory afferent volleys. Evoked potentials were recorded from the exposed vermal surface of the cerebellum. Using two stimulators, we applied two stimuli of different modality at different time intervals. It was found that if the two volleys arrived at intervals of not more than approximately 10 msec., mutual facilitation occurred. The ''primary'' positive-negative deflection was enhanced. Superimposed spike components were also enhanced, or, if not present in the control records of either evoked potential, appeared if both stimuli were given. If the volleys arrived at intervals of from about 20 up to 300 msec., the second of the evoked potentials was inhibited. Such interaction phenomena were observed for the following combinations of stimuli: acoustic-optic, acoustic-''tactile'', and optic-''tactile''. In addition, interaction was observed if (physiological) acoustic stimuli were combined with afferent volleys induced by stimulation of the cerebral visual projection area and also with the optic ''off'' response.

15. Correlation between monosynaptic reflex activity and EEG during short barbiturate anesthesia under normal and pathological conditions. — ALBRECHT and ELIZABETH STRUPPLER, Munich, Germany.

There is correlation between brain-wave activity and peripheral and central reflex excitability in man. During light anesthesia (Thiogenal: Merck) we found: 1. During the initial state of anesthesia, when the EEG slows down to delta and theta activity in all leads, there is a corresponding decrease of tendon reflexes (ankle-jerk). 2. During the phase of frontal beta activation, the tendon reflexes decreased (sometimes) to zero, and normal muscle tone disappeared. 3. When consciousness returns, the tendon-reflex activity and the occipital brain-wave activity comes back to normal values, but the frontal EEG changes persist longer. 4. During sensory stimuli (acoustic) or cerebral activity (as in calculation) there is definite increase in tendon-reflex activity during the alpha inhibition. The excitability of the motor neurone itself (independent of muscle-spindle activity) differs from the tendon reflexes and the EEG.

The relation of the reticular formation to the cortex, the blocking of alpha, and the gamma-motor-system (Granit) are discussed. Findings on patients with involuntary movements are compared with normals.

16. Condition specific electro-oculographic measures of fatigue. — CHRISTINE KRIS, Boston Lying-in Hospital, Boston, Mass.

17. Electroencephalographic determination of barbiturate susceptibility in chronically adrenalectomized hormone supported cats, a preliminary report. — HUNTINGTON MAVOR, STEWART COOK and W. F. CHAMBERS, U. of Vermont College of Medicine, Burlington, Vt.

We have attempted to determine the minimal intravenous doses of Pentothal and pentobarbital necessary to produce ''spindling'' in the electrocorticograms of normal cats as compared to adrenalectomized cats supported for periods of 4-5 weeks with optimal doses of either cortisone or desoxycorticosterone acetate. Cats with altered adrenal states were found to be approximately twice as susceptible as normal cats to both Pentothal and pentobarbital. Using bipolar scalp recordings, with pentobarbital anesthesia similar results were obtained. The effects on the EEG of rostral reticular stimulation following small increments of pentobarbital were noted in normal and in altered adrenal states. The development of progressive EEG synchronization with accumulative low doses of pentobarbital coincided with the progressive ineffectiveness of rostral reticular stimulation in causing cortical activation. The effects of rostral reticular stimulation were abolished in the hormone supported cats at doses of pentobarbital approximately one-half those required for normals.

18. Unitary analysis of the response elicited in the visual cortex of cat. — L. WIDEN and C. AJMONE MARSAN, NIH, Bethesda, Md.

Experiments were performed with tungsten microelectrodes in the cortex and underlying white matter of the visual area in nembutalized cats. Responses were evoked by electrical stimulation of optic radiation.

The majority of spike potentials recorded in these experimental conditions are temporally related to the primary, specific evoked surface response.

Almost all spikes recorded during the first or second waves are picked up from the underlying white matter and all of them have pre-synaptic characteristics as tested by double shocks and high frequency stimulation.

The spikes recorded during the 3rd wave have the most extensive spatial distribution being found in both cortex and white matter. Some behave as pre-synaptic; others as post-synaptic phenomena.

The spikes recorded during the 4th and the rare ones temporally related to the 5th wave, all are of a post-synaptic type and most of them are only found within the cortex.

There is a positive correlation between presence of spike and amplitude of the surface response. The relationship can be expressed as follows: a first or second wave spike appears when the 1st or 2nd wave have reached a critical size. The spike then remains stable, responding to every stimulus.

A third wave spike of pre-synaptic type behaves in the same way. Spikes of post-synaptic type, related to 3rd, 4th or 5th waves also appear when the 1st wave; (i.e. the afferent volley) has reached a certain size. Above this threshold value, however, they remain ''unstable'' responding in an irregular way to stimuli of constant strength. Under these circumstances the probability of discharge is greater, the larger the amplitude of the late surface waves.

These findings provide further confirmation of some of the commonly offered interpretation on the nature of the various components of the surface response. They also provide an explanation of the difference of opinions still existing in regard to the nature of wave 3. This is considered post-synaptic by some and pre-synaptic by other investigators. On the basis of our findings both pre- and post-synaptic components are present in wave 3.

19. Comparison of EEG activity recorded from different locations on the scalp by means of autocorrelation and crosscorrelation analysis. — JOHN S. BARLOW and MARGARET Z. FREEMAN, Massachusetts General Hospital and M. I. T., Cambridge, Mass.

A quantitative measure of the degree of rhythmicity of EEG activity, averaged over a predetermined interval of time (e.g. 1 min.), can be obtained by

autocorrelation analysis. Similarly, an indication of the existence of components common to two locations on the scalp, as well as the relation in time between them, can be obtained by crosscorrelation analysis. For example, the average phase relation between the activity at two locations that exhibit the same dominant rhythm can be derived. Contrariwise, the frequencies of activity records from different areas can be clearly differentiated, even when they differ by only a small amount, with the use of these techniques. Some results of these studies for a group of normal subjects and for a small number of patients with disease of the brain will be presented and discussed in relation to concepts of cerebral pacemakers.

20. A comparative study of sphenoidal needle and pharyngeal electrodes in the EEG of patients with temporal lobe seizures. — R. L. Rovit, P. Gloor and L. R. Henderson, Jr., Montreal.

Discrete lesions of the mesial aspect of one temporal lobe, particularly in the amygdaloid and uncal areas, are frequently the cause of focal cerebral seizures. If patients with such discrete lesions are to be considered as candidates for surgical therapy, electrographic localization of the discharging focus must be precise and unequivocal.

Methods for recording from the basal and mesiobasal aspect of the temporal lobe have been devised and are in use in various centers. Among these methods are the use of pharyngeal electrodes, tympanic electrodes and insulated needles inserted beneath the sphenoid bone. Each specific technique has its adherents. However, no sufficiently large series of cases have been studied in which pharyngeal and sphenoidal electrodes have been used simultaneously and their comparative usefulness assessed.

We have investigated a series of patients, with the clinical manifestations of temporal lobe seizures, by recordings simultaneously from the convexity and from certain predetermined positions on the base. Standard pharyngeal electrodes and deep sphenoidal electrodes have been used in every case and their exact position verified radiographically. The anterior sphenoidal electrode was placed just lateral to the Pterygo-palatine fossa and a posterior sphenoidal electrode just lateral to the foramen ovale. Thus electrographic recordings have been obtained from three separate positions on the mesial surface of each temporal lobe.

Methods and techniques of needle placement and recording will be outlined and certain preliminary observations resulting from this study will be discussed.

21. The familial occurrence of electroencephalographic abnormalities involving the temporal areas (Preliminary Report). — E. A. Rodin and J. Whelan, Wayne State University, Detroit, Mich.

During the past year routine electroencephalograms were obtained on 12 normal volunteer families and 32 families where at least one member suffered from a convulsive disorder or psychiatric disturbance. The families consisted of parents and their children. Grandparents and distant relatives were excluded. It was noted that in certain instances electroencephalographic abnormalities in the temporal areas were present in similar fashion in more than one member of a family. In adolescent patients with temporal lobe disturbances corresponding electroencephalographic findings could be seen in one parent, while in cases of adult patients with temporal lobe convulsive disorders, the EEG of one of their children might likewise show a temporal focus. The nonpatient family members were clinically asymptomatic and there was no overt neurological cause for the EEG changes. The most common temporal EEG abnormalities were shifting complex theta and sharp wave discharges. Illustrative case material will be presented.

22. Microelectrode studies of temporal cortical unit activity during amygdaloid seizures in the cat. — G. Yamamoto and H. H. Jasper, Montreal Neurological Institute, Montreal.

23. A flash evoked electroencephalographic response permitting detection of minor degrees of light sensitivity in man. — C. Wesley Watson, John Hunter, Patricia Wanning and Reinette Bowker, Boston, Mass.

This paper describes a previous unemphasized electroencephalographic sign of light sensitivity which assists in anticipation of impending seizure during photic stimulation; diagnosis of seizure susceptibility without structural basis, particularly where asymmetrical excessive discharges occur; and the exclusion of light sensitive individuals from occupations in which flashing light is an indigenous hazard, e.g. helicopter operation.

Component and distribution analysis was undertaken of the various light evoked electroencephalographic responses in the inkwriter traces of 285 light sensitive individuals comprising 101 subject to seizures and 71 relatives.

A three component, ca. one second duration response, originating posteriorly and often asymmetrically, was identified. The response occurs early or terminally in relation to repetitive flashing. With favorable stimulation it underwent gradual transformation and became generalized as the familiar polyspike and slow wave discharge often accompanied by myoclonic seizure phenomena. It comprises a surface negative slow wave (ca. .3 sec.); a complex positive deflection (ca. .06 sec.) and a high amplitude (up to ca. 100 μV. above baseline) negative slow wave (ca. .6 sec.) of complex composition.

Possible mechanisms of production and relation to other characteristic responses to repetitive flash in light sensitive individuals will be discussed.

24. Anosognosic seizures: their clinical and EEG correlates. — Robert S. Schwab, Boston, Mass.

We have recently been perturbed by finding, in a nurse with grand mal spells which were fully controlled by Dilantin and phenobarbital, that her regular visits reporting no spells were in error. Her sister, a nurse with whom she lives, came in and described three minor automatisms that she had noted, lasting under 30 sec., of which the patient had no recollection and was completely unaware that she had had them. These later were brought under full control by changes in her medication. We have encountered ten other patients whose major seizures were under complete and long-term control, but who had from time to time brief spells of which they were completely unaware.

When these brief spells are of the petit mal pattern, i.e. simple loss of awareness without any

motor activity, the electroencephalogram usually shows spike and wave seizure patterns, and the spells can therefore be readily identified. With the spells involving vocalization and chewing movements and automatisms, the EEG in between spells may be perfectly normal. We feel that these could be better identified if they were specifically looked for during the visits of epileptics under otherwise good control.

THE DUTCH EEG SOCIETY

Wilhelmina Gasthuis, Amsterdam

March 7, 1959

Secretary: O. MAGNUS
St. Ursulakliniek, Wassenaar, Holland

1. Statistical relations in the duration of some patterns in the EEG. — A. Strackee-Kuijer, J. J. Denier van der Gon and J. Strackee, Heemstede and Amsterdam.

The durations of some specific EEG patterns have been measured. These patterns were: 1, the paroxysms of bilateral synchronous spikes and waves; 2, the intervals between them; 3, bursts of alpha waves; 4, the intervals between them; 5, the intervals between the typical discharges of subacute leucoencephalitis.

The number of measurements varied between about 100 and 1000 in an EEG.

We could not detect correlations between: the sequential durations of the discharges; the sequential durations of the intervals; the duration of a discharge and that of the following interval; the duration of an interval and that of the following discharge. I.e., There is no influence on the duration of the pattern by the past events.

For each EEG containing alpha bursts or paroxysms of spikes and waves two histograms were made: (*a*) the number of discharges lasting a certain time; (*b*) the number of intervals lasting a certain time.

Of the EEG's of the subacute leucoencephalitis only the last histograms were made. All these histograms differed from a normal probability curve as they were more or less skew. As the histograms could not be described with an exponentially decaying function, the probability of termination of the phenomenon must depend on the time of onset of the phenomenon. Therefore it appears that there have to be processes which start at the moment the phenomenon starts. This holds for the discharges themselves as well as for the intervals.

Because the probability of termination increases with time and in our material never becomes a constant, the processes, which start at the moment the phenomenon starts apparently exert influence up to the end of the phenomenon.

2. EEG during heart operations with extracorporeal circulation. — W. Storm van Leeuwen, L. Kok and E. Zierfusz, Leiden.

During 60 heart operations with extracorporeal circulation an EEG was recorded. The recording started immediately after the patient was anaesthetized and was stopped when the operation was finished (4-14 hours). Eight electrodes were sewn into the scalp. An automatic frequency analyser (Walter) was used. The EEG apparatus was stationed outside the operating theatre. The operation could be followed visually by means of a window in the wall and a mirror about 3 feet above the patient and acoustically by an intercom system.

The "normal" EEG (taking into account the anaesthesia) usually consists of beta and theta and increase of delta activity up to 200-400 μV.

Cerebral anoxia is also causing the occurrence of delta waves with low frequencies and high amplitudes. Serious anoxia quickly causes electrical silence.

The EEG proved valuable in spotting cerebral anoxia.

The automatic frequency analysis proved useful in evaluating the frequency content of the EEG.

3. The significance of the EEG in cerebro-vascular disorders. — J. H. A. van der Drift and O. Magnus, Wassenaar.

This study concerns 200 cases of ischemic disorders of circulation, 77 cases of intracerebral hemorrhage, 40 cases of subarachnoidal hemorrhage and 30 cases of diffuse cerebral vascular disorders. The diagnosis was partly verified by operation or autopsy, partly made by clinical and angiographic investigations.

In ischemic disorders the most extensive focal abnormalities were found in cases with occlusion of the internal carotid artery and of the superficial branches of the medial cerebral artery. With a few exceptions these abnormalities were strictly unilateral. Occlusion of the posterior cerebral artery and of the anterior cerebral artery showed less marked focal abnormalities. Occlusion of the deep branches of the medial cerebral artery and of the basilar artery did not give rise to focal EEG abnormalities.

In most cases there was a difference in the EEG between the abnormalities found in cerebral thrombosis and in cerebral embolism. The last cases showed more extensive and longer lasting delta activity and more epileptiform activity. The abnormalities found in cerebral hemorrhage were predominantly determined by the site of the lesion and not by its cause. In contrast with the capsular thrombosis the capsular hemorrhage caused marked focal EEG abnormalities.

The EEG disorders in cerebral hemorrhage usually were more extensive and not so strictly unilateral as in ischemic vascular disease. The abnormalities found in a pure subarachnoidal hemorrhage are considered to be due to a disturbance of the higher brain stem.

In diffuse cerebral vascular disorders apart from other abnormalities, bilateral intermittent rhythmic delta activity maximal at the frontal pole was often seen.

PRINTED IN CANADA

BOOK REVIEWS

Edited by CHARLES E. HENRY

THE EXCITABLE CORTEX IN CONSCIOUS MAN

WILDER PENFIELD

Charles C. Thomas, Springfield, Illinois, 1958, 43 pp., $2.50

"A clinician must contribute to Science as best he can from very different material and as chance presents it. The brain and the mind of man constitute evidence that is denied to the experimental physiologist. Man talks and thinks for himself, and that constitutes our great opportunity. But the physiological clinician cannot control experiments nor plan them. Disease and stress and accidents perform experiments on the brain of men and women and children. We can only wait and watch and rationalize, as opportunity presents itself. All operations reported here were practical attempts to help patients, most of whom were suffering from focal epileptic seizures. Seizures were stopped in about half the cases."

In this way Penfield introduces a 40-page summary of his years of magnificent work on the stimulation of the human cortex. The great virtue of this work is that he has approached each of his hundreds of craniotomies, not only therapeutically as a surgeon, but scientifically as a physiologist and psychologist who observes carefully and makes extensive records at the time. He would probably disclaim any right to be called a psychologist, but his observations have brought important data to that field.[1] Penfield's beautiful records with charts, photographs and electroencephalograms have been the basis of a long series of important papers. The present little book reviews two aspects of his work: the results of cortical stimulation and his hypothesis of a centrencephalic integrating system.

The results of human cortical stimulation are summarized modestly and almost too briefly. Useful drawings are reproduced and adequate references to detailed researches are given. The location in man of supplementary and secondary sensory areas, and of visceral sensation, as well as the descriptions of a supplementary motor area, and refinements of observations in the classical motor and sensory areas, are original contributions, well known by now and corroborated by repetition and by other observers. This map-making is not done in the definitive way of 30 years ago. Penfield understands well the variability of response of the different areas and describes it. But maps are disturbing to some of his critics, notably Walshe. One cannot discuss Penfield's contribution without taking cognizance of Walshe's attack in 1957, which perhaps caused Penfield to put his soft answer in the form of the present Sherrington Lecture. Sir Francis wields a weight and witty pen, and with it he has intimidated a generation of neurologists. But that is no reason why we should quietly accept such intolerant and destructive attacks without protest. For example: in one of Penfield's earlier papers on localization of motor function, he published a diagram of the cortex in which the motor area is graphically depicted as a homunculus with big face and lips and hands and a small body. This has been useful in teaching because it strikingly illustrates some physiological truths; it is knowingly diagrammatic and carefully labeled as such. Yet Sir Francis blasts it as a "reversion" to "medieval heraldry". The exhibition of such editorial bad taste makes one wonder if some "homunculus" might not be sitting in Sir Francis' frontal lobes, taking possession of him whenever he begins to write and compeling him to show off his pretty wit. Moreover, this criticizing paper is not above criticism. Walshe's resurrection of Carpenter's ideas concerning the physiology of the brain seems about as pertinent as a review of Leonardo da Vinci's aeroplane plans would be for modern aviation. Nor does this reviewer believe the statement that "neither Jackson nor Sherrington accepted mental activity as a function of the nervous system".

Be that as it may, Penfield's observations over a quarter of a century stand as a permanent monument; interpretations and hypotheses change with the advancing knowledge of the time, but observations are immortal.

The observation that "psychical responses" (page 20) could be elicited by stimulation of parts of the temporal cortex is something entirely new. Under this term Penfield includes "experiential hallucinations" and "interpretive illusions". The former are complete bits of past experience, vivid little scenes both seen and heard like dreams, but to the patient they are not completely real; he knows they are memories and reports them as such. The latter are illusions of perception; the patient when stimulated by the electrodes reports that "things seem unfamiliar" or too familiar, or too large or too small. These illusions also are only elicited from the temporal

1 I applaud Tolstoï's words of 1875 — "Is there a line to be drawn between psychological and physiological phenomena in man ? If so, where ?" (Anna Karenina, part I, chapter VII).

lobe cortex, and their resemblance to auras of temporal lobe fits is striking. It is also remarkable that Penfield has been able to elicit experiential hallucinations only from the temporal lobes of epileptic patients, and only in 37 of the epileptics upon whom he has operated. This fact, though striking, does not make the observations less important; a few positive experiments are more interesting than hundreds of negatives. The facts of these stimulation experiments added to the observation that bilateral removal of the inferior mesial zones of both temporal lobes interferes with memory (page 36) makes it obvious that the temporal lobes and their central connections are important organs for the mechanism of memory recall.

Another contribution arising from Penfield's cortical stimulations is his demonstration that electrical stimulation of a gyrus in a sensory region of the cortex, even when completely circumcised, i.e. when cut off from all lateral association with other cortical areas, causes the patient to report sensation. He believes that impulses induced in this way return to subcortical structures by way of long corticofugal fibres. This taken in conjunction with the observation by Penfield (page 8) and other neurosurgeons, that small lesions in the brain stem cause more interference with consciousness than lesions of the cortex, gave rise to his theory of a ''centrencephalic system'' in the diencephalon.

In my opinion, the surgical observations do not prove that the brain stem has a major role in producing consciousness; they may only indicate that the neuron circuits responsible for this state of mind are most vulnerable in that region, probably because a small lesion can, at that level, injure more of them. As these circuits spread out to many parts of both hemispheres they become less vulnerable to small lesions, but they are no less important to consciousness. I believe that here in the cerebral cortex is located an essential mechanism for the receptive function which I have elsewhere (Cobb 1952) called the discriminative part of consciousness. I do not believe that ''large areas of cerebral cortex could be removed without loss of consciousness.'' (page 8). Of course they can be removed without causing stupor or coma, but refined psychological tests show that cortical removals reduce that attentive and discriminative awareness which I consider an important part of consciousness.

Penfield's observations and theory are of importance whether or not one agrees that this centrencephalic system is the great integrator. At least one can think of these long feed-backs as indispensable to the complicated cerebral functions.

The ''psychical responses'' elicited by Penfield are a quite different sort of phenomenon from simple memory traces (Thorpe 1956), the basic function of nervous tissue that provides for reaction in the light of past experiences. Until this basic memory mechanism is understood one cannot hope to understand the scenes from the past evoked by stimulation of the human brain. The mechanism by which memories are stored is still a mystery.

These are the observations; a discussion of the hypotheses is quite a different thing. Here, matters of emphasis and opinion come in, and Penfield emphasizes that when ultimate truth is known, present philosophies will largely disappear (page 4). With several of Penfield's conclusions I do not entirely agree, and I admit that this difference in theory is of little importance as compared to Penfield's discoveries. Nevertheless, discussions bring up problems for investigation and have their place in scientific endeavor. Many of Penfield's data were well described in his paper at the symposium on ''The Neurological Basis of Behavior'' (Wolstenholme and O'Connor 1958); and they were thoroughly discussed at that meeting by a group of brilliant neurologists. My own points are as follows:

On page 7 Penfield gives his hypothesis: ''Let us assume that there is a system of nerve fibre tracts and of gray matter within the higher brain stem which plays the major role in the organization of the functions of the two hemispheres.'' I believe that this is a sound and useful assumption except for two words — ''the major''; I would rather say ''an important role''. ''The organization of the functions of the two hemispheres'' seems to me to be important for mind and consciousness. The sections of the corpus callosum by Van Wagenen reported by Smith and Akelaitis in 1942 proved that a large part of the coordination of the functions of the two hemispheres must take place by way of tracts from cortex to striatum or diencephalon. Since then the extensive work on the reticular formation of the brain stem emphasizes the importance of this region in relation to cerebral function. But I see no reason for believing that the ''higher brain stem'' plays the ''major role''.

To me it seems that the ''centrencephalic system'' is a useful concept, a good ''working hypothesis'' as Penfield calls it, to help explain the phenomena of consciousness and memory, but, from its very nature it must be a connecting system that integrates impulses from the hemispheres, and thus cannot be confined to the diencephalon, mesencephalon and metencephalon, because an essential part of the system is the series of long circuits that reach out to the cortex and return therefrom. There are, no doubt, also many short circuits within the brain stem. But to me the complex and varying phenomena of consciousness and memory can only be explained by an hypothesis of

many circuits, large and small, integrated at all levels of the neuraxis and including transcortical and callosal connection. It is indeed a picture of wheels within wheels, but one does not need to be troubled by the whirling complexity of the picture.

The reflexology of the first quarter of this century, with its concept of the nervous system as an overgrown switchboard with specific centers, was too simple. It has been surpassed by the new knowledge of reverberating circuits, feed-back systems and the central modulation of sensory perception. A new picture of the activity of the brain emerges: a picture of a forebrain alerted to receive selected stimuli by mechanisms in the brain stem, which can in turn influence peripheral sensory input. Each of these levels acts on the others by signals from internuncial circuits. Such a concept of cerebral processes gives an idea of large patterns of excitation with continuity and rhythm. It explains the function of many neurons and short tracts that until recently had anatomical names but no meaning. The centrencephalic system is an important part of all this, but such functions as memory and consciousness are too fundamental to be localized in any one system. Memory is a fundamental function of even simple integrations of neurons, because it is the function that allows for reaction in the light of past experience. Consciousness is a part of mind that emerges gradually during the course of the phylogenetic evolution of the brain, appearing in its full human form only when the brain has attained an enormous complexity. Such functions are certainly more dependent on the integrity of some parts of the brain than on others, but in my opinion, they cannot be localized in any one system or small group of anatomical systems.

STANLEY COBB

REFERENCES

COBB, S. *Epilepsia,* Third Series, Vol. T, November, **1952.**

SMITH, K. V. and AKELAITIS, A. J. *Arch. Neurol. Psychiat.,* Chicago, **1942,** *47*: 519.

THORPE, W. H. *Learning and Instinct in Animals,* Chapter VII, Harvard University Press, Cambridge, Mass., **1956.**

WALSHE, FRANCIS, M. R. (Sir). *Brain,* **1957,** *80*: 510.

WOLSTENHOLME, G. E. W. and O'CONNOR, C. M., Editors. *The Neurological Basis of Behavior,* The Ciba Foundation Symposium in London, July 2-4, **1957,** Little Brown & Co., Boston, **1958.**

ANNOUNCEMENT

BOARD OF QUALIFICATION

The Board of Qualification of the American Electroencephalographic Society held its annual examination in Baltimore, Maryland on June 9, 1959. The following candidate was qualified:

Dr. ROBERT J. JOYNT, Iowa City, Iowa.

The next written examination will be given in early March, 1960. This portion of the examination is given in the candidate's home city. The oral and practical portion of the examination will be given in Hartford, Connecticut in early June, just preceding the meeting of the American EEG Society in Boston. Completed applications for examination must be submitted by February 1, 1960.

The present Board of Qualification is as follows:

Chairman: JEROME K. MERLIS, Baltimore
Secretary: CHARLES E. HENRY, Hartford
CURTIS MARSHALL, Baltimore
A. EARL WALKER, Baltimore
RICHARD P. SCHMIDT, Gainesville

Information and application forms may be obtained from the Chairman at

University Hospital, Baltimore 1, Maryland.

PRINTED IN CANADA

RETICULAR FORMATION OF THE BRAIN

HERBERT H. JASPER, LORNE D. PROCTOR, ROBERT S. KNIGHTON,
WILLIAM C. NOSHAY and RUSSEL T. COSTELLO, Eds.

Little, Brown & Company, Boston, 1958, 766 pp., $16.00

In March 1957 a Symposium on the Reticular Formation was held at the Henry Ford Hospital (Detroit, Mich.). Only four years had elapsed since the St. Marguerite Symposium, but the Co-chairmen of the Local Program Committee, Drs. Knighton and Proctor, thought that the enormous amount of work performed during this period deserved to be discussed in an international meeting of neuroanatomists, neurophysiologists, neuropharmacologists, experimental psychologists and clinicians. This volume, published under the auspices of the Henry Ford Hospital, contains the papers and discussions of the Detroit Meeting, and is the best evidence that Drs. Knighton and Proctor were justified in proposing the Symposium subject.

The book starts with two outstanding anatomical contributions, devoted to the hodology (Nauta and Kuypers) and synaptology (A. B. and M. E. Scheibel) of the brain stem reticular formation. Nauta and Kuypers point out that extralemniscal sensory pathways, arising from the spinal cord and the trigeminal sensory nuclei, mix inextricably with the ascending reticular fibers. The importance of these facts for the physiologist hardly requires emphasis. They stress the need of a physiological analysis to differentiate the ascending reticular system from the extralemniscal sensory paths. These paths are obviously costimulated whenever electrical pulses are applied to the reticular formation, and the bilateral section of the *lemnisci* at midbrain level will abolish neither the tonic nor the phasic effects exerted on the cerebrum by the volleys ascending along them. Experiments published after the Detroit Symposium[1] may represent a first step in this direction. Although the diffuse tegmental pathways arising in the spinal cord and in the sensory nuclei of the trigeminus are severed to the same degree after midpontine pretrigeminal transection and complete midbrain section (Bremer's *cerveau isolé*), only in the latter preparation are the well known EEG sleep patterns observed. In the midpontine pretrigeminal cat EEG activation patterns actually predominate, a fact suggesting that the tonic activity of somata lying in the upper pons has a critical importance for the maintenance of wakefulness. A great stimulus to reticular physiology will be provided by the findings of Nauta and Kuypers on the ultimate distribution of long ascending reticular fibers not only to the subthalamus and the intralaminar nuclei of the thalamus, but also to the hypothalamus, to the limbic system and to the basal ganglia. Massive reciprocating connections are described, moreover, between the hippocampal system and the reticular structures of the midbrain. These data suggest a wealth of experimental approaches to the investigator. Incidentally, they imply, in the reviewer's opinion, that the midline nuclei of the thalamus represent merely one of the structures influenced by the reticular formation of the brain stem, and it may be misleading to stress this connection to the exclusion of the others.

The Scheibels summarize the results of seven years of work devoted to a study of the reticular formation with the Golgi method. Their beautiful illustrations show some data which could have been predicted from physiological observations, such as the tremendous convergence of afferent axons onto reticular neurons. But here again a wealth of new morphological findings confronts the physiologist with entirely new problems. There is a surprising tendency for the collaterals of the spino-thalamic and pyramidal tracts, as well as the arborizations of the dendrites of the reticular neurons to be organized in planes approximately perpendicular to the long axis of the brain stem. Golgi type II cells are lacking in the brain stem reticular core, a fact which does not fit the physiological hypothesis of chains of short-axoned cells, although the richly branching collaterals given off by the long reticular axons maw well subserve the same purpose. Some results obtained with newborn rats or mice represent a fascinating achievement of the Golgi technique, since axons arising in the rostral magnocellular portion of the medulla have been followed up to the diencephalon, and are seen to send collaterals not only to the intralaminar nuclei but also to the specific relay nuclei of the thalamus. Finally the large medullo-reticular cells whose axons project both rostrally and caudally may represent one of the means of correlation between ascending and descending reticular systems.

The point of view of comparative neuroanatomy is presented by one of its greatest leaders, Dr. C. J. Herrick, in collaboration with Geo. H. Bishop. They compare the amphibian and mammalian lemniscal systems and deal with their relation to the reticular

[1] BATINI, C., MORUZZI, G., PALESTINI, M., ROSSI, G. F. and ZANCHETTI, A. *Arch. ital. Biol.*, **1959**, *97*: 1.

formation. Other considerations, mainly based on comparative neuroanatomy, are presented by Bishop in a separate report.

The physiological material starts with a report by Amassian and Waller. By timing the spike discharges of reticular units with an electronic chronometer they found that the mean number of discharges, their latencies and the duration of the interspike intervals differed in certain reticular neurons depending upon the part of the body surface which was stimulated. Hence, afferent convergence is not necessarily accompanied by a loss of information concerning the peripheral source of the afferent volleys, and space in the periphery is partly coded centrally in the timing of the repetitive response. They think that these reticular cells may be related to local behavioral responses or to local sign in perception. The generalized functions of the reticular formation may be performed by other neurons, with wide receptive fields, which respond similarly to different afferent sources.

Livingston reviews the fascinating problem of brain stem control of afferent activity, a field of investigation that has been at the center of neurophysiological endeavour since 1952, when Granit and Kaada discovered that reticular stimulation exerts a striking influence on the central control of spindle discharge. Livingston points out that whenever sense organs or second and third order sensory neurons were shown to be under the control of the central nervous system, either (i) the reticular formation or (ii) central structures known to be associated with it were found to be capable of this influence. In the reviewer's opinion, the evidence for (ii) should not be regarded as convincing proof that this control, including the phenomena of habituation and sensory attention so brilliantly investigated by Hernández-Peón and his colleagues, belong exclusively, or even predominantly, to the reticular formation. This has indeed been the prevailing trend of thought during recent years, although in the pioneer work of Granit and Kaada it had been clearly stated that muscle spindles could be influenced by stimulating several other structures, like the cerebellum, the motor cortex and the pyramidal tract. It has been shown recently (i) that the midbrain points whose electrical stimulation inhibits the auditory response of the cochlear nucleus lie outside the reticular formation [1] and (ii) that habituation of visual responses can be easily obtained when all the bulbo-pontine and part of the midbrain reticular formation has been disconnected from the cerebrum by a postcollicular transection.[2]

Two contributions, by O'Leary, Kerr, and Goldring and by Arduini, deal with D.C. recording from the cerebral cortex during stimulation of the midline thalamic nuclei and of the brain stem reticular formation. The first group, working on pretrigeminal rabbits, shows that an enduring surface-negative shift is initiated in the frontal areas by high rate stimulation of the midline thalamus and of the midbrain reticular formation. Arduini starts with a summary of his experiments with Mancia and Mechelse (1956, 1957). They found that the EEG arousal elicited by sensory stimulation was accompanied, in the unanesthetized cat, by a surface-negative potential oscillation all over the dorsal aspect of the cerebrum, a phenomenon which was shown to be neural in origin and probably mediated by the ascending reticular system. These D.C. shifts were observed also during experiments of reticular and thalamic stimulation he performed with Brookhart *et al.* However the enduring potential changes elicited by reticular stimulation, like those occurring during sensory arousal, could be recorded from the entire dorsal aspect of the cerebral cortex, while the surface-negative shifts elicited by high rate stimulation of the midline and relay nuclei of the thalamus were strictly localized to the same areas which show recruiting and augmenting responses during 8-10/sec. stimulation of the midline and relay nuclei respectively. Hence there is a rather unexpected difference between the brain stem reticular formation and the so-called diffuse projection nuclei of the thalamus, even when the same parameters of electrical stimulation are applied. It follows that the well known spatial limitations of the recruiting responses cannot be ascribed simply to the inability of low rate (8/sec.) stimulation to overcome synaptic resistances within the thalamic structures, another finding which tends to argue against the inclusion of the midline thalamic nuclei within the ascending reticular system.

In reviewing his work with Ricci and Doane on the discharge of cortical units of the unanesthetized monkey, Jasper states that "the so-called arousal patterns of the EEG may be associated with complex inhibitory and excitatory changes in unit cell discharge within the cortex", a conclusion that fits previous results obtained with other animals and in different experimental conditions. He rightly emphasizes that if the reticular system is important in the process of consciousness, "it must possess properties of differential organization. In this process, inhibitory mechanisms probably play a leading role". The fine technique developed by Jasper, Ricci and Doane lends itself admirably to an analysis of this differential organization of the ascending reticular system in the unanesthetized animal with full integrity of the central nervous system. It is to be

---

[1] Desmedt, J. E. and Mechelse, K. *C. R. Soc. Biol.*, **1957**, *151*: 2209.

[2] Mancia, M., Meulders, M. and Santibañez, G. *Arch. ital. Biol.*, **1959**, *97*, in press.

hoped that further work will be done along these lines of investigation. Similar views had been put forward in the final discussion of the St. Marguerite Symposium and at the Brussels Congress, and Anokhin has recently reported evidence showing that there might be several types of EEG arousal. The problem of whether the ascending reticular system is concerned exclusively with providing an unspecific facilitatory influence or if it is endowed with a more subtle and differentiated organization is one that might be solved eventually only by multiple microelectrode recording from the reticular formation and the cerebral cortex of the unanesthetized animal.

Dell summarizes the important observations made by him and his associates. He recalls that adrenaline arousal, but not hypercapnic arousal, is abolished by a prepontine transection, while the EEG effects of increased pCO_2 are no longer observed only if the midbrain is disconnected from the cerebrum. An elegant demonstration that the reticular neurons which regulates respiration have the same sensitivity to CO_2 as those belonging to the ascending reticular system is provided by Dell's preparations with a pontine transection, in which inhalation of CO_2 produced EEG arousal and increased phrenic discharge at the same time. Dell's hypotheses of the adrenergic mechanism in reticular arousal and of the translation of bodily needs into behaviour are vigorously expressed, and appear undoubtedly to be supported by several lines of indirect evidence. However, recent observations [1] showing the absence of EEG arousal following intra-arterial injections of adrenaline and nor-adrenaline, in doses large enough to produce a contraction of the nictitating membrane stronger than that elicited by activating intravenous doses of the catecholamines, cannot be easily reconciled with this hypothesis. One should not forget, moreover, that the EEG arousal is usually obtained with high intravenous doses of adrenaline or following strong nociceptive stimulations. It would be interesting to ascertain, quantitatively, whether the oversecretion of adrenaline elicited by hypoglycemia in the fasting animal is indeed adequate, as Dell has suggested, to produce EEG and behavioural effects. Of course these difficulties should simply stimulate the physiologist to carry on further investigations starting from Dell's observations, which have been repeatedly confirmed and whose importance appears to be great whatever the ultimate interpretation will be

Ingvar deals with an extremely interesting field of investigation, that of the cortical circulatory changes occurring during EEG arousal. With Söderberg he has found, in Granit's laboratory, that an increase of cortical blood flow, exclusively due to local decrease of vascular resistance, occurs in the *encéphale isolé* following reticular stimulation. This effect is always secondary to the EEG arousal, and usually the cortical blood flow comes back to its prestimulatory level when the first spindles reappear. Both phenomena are shorter in duration and less pronounced in the *cerveau isolé*. It is well known that reticular stimulation occasionally elicits the so-called "flattening reaction", i.e. the spindles disappear without being replaced by low voltage fast activity. In these cases the circulatory changes are absent, and Ingvar suggests that only true cortical activation gives rise to an increase of oxygen consumption and thus of the output of CO_2. The circulatory phenomena are probably related with local metabolic changes of pCO_2.

The important results obtained by the Freiburg group in several years of work devoted to a microelectrode analysis of the visual cortex are summarized by Jung. It is well known that these investigators have found five groups of neurons in the visual cortex of the cat, the distinction being based upon their response to photic stimulation. Types B, D and E, three of these cell groups, correspond to the on, off and on-off units of the retina respectively. Neurons A are unaffected either by light or darkness, while group C show on and off inhibition when short flashes are applied and appear to be unaffected by prolonged darkness or illumination. The light-responsive B, D, E neurons and even the A units are driven during recruiting stimulation of the midline nuclei of the thalamus. The A-neurons, though they do not respond to light as such, may show different reactions in light and darkness, while the critical fusion frequency of the B units is heightened following thalamic or reticular stimulation. Jung concluded that the non-specific system "may induce increased readiness of cortical neurons to respond to series of afferent impulses that cannot be followed without thalamic or reticular stimulation". This fine example of a facilitating influence exerted by the ascending reticular system on specific functions of the cortex should be correlated with the recent results obtained in Bremer's and Dell's laboratories and with the studies of Lindsley, to be reported below.

Purpura's report concerns the excitatory and inhibitory synaptic mechanisms of the cerebral cortex. The reader is refered to the Symposium on dendrites which is published in the 10th Supplement of this Journal for a more recent presentation and discussion of the results obtained by the group at the Columbia University. It is difficult for those who do not have direct experience in this field to express an opinion, not on the factual data, which have been confirmed and are incidentally documented in this report by

[1] MANTEGAZZINI, P., POECK, K. and SANTIBAÑEZ, G. *Arch. ital. Biol.*, **1959**, *97*, in press.

several good records, but on their interpretation. On the whole one remains with the impression that the author has a tendency to rely too much on pharmacological evidence. Since the time of Claude Bernard it has always been the hope of the physiologist to make what has been called a functional dissection by the use of suitable drugs; and there is little doubt that results of the greatest importance were achieved whenever strict specificity of pharmacological action was demonstrated. To provide this demonstration is not always easy, however, and mainly for this reason some physiologists would not agree with some of the interpretations offered in Purpura's report. Because of space limitations only two examples of this possible divergence of views are given below. Strychnine by no means blocks all inhibitory effects, as shown e.g. by the fact that the inhibition elicited by electrical stimulation of the cerebellar anterior lobe is present, and possibly enhanced, after intravenous injection even of tetanizing doses of the drug [1, 2, 3]. On the other hand the fact that no convulsive "spikes" can be detected following local application of the convulsant drug does not imply that it is impossible to stimulate the underlying neurons with this procedure. As a matter of fact cerebellar excitation by local strychnine has been demonstrated in several ways [4], even in non-decerebrated animals [5, 6], while there is convincing evidence that inhibition by hyperpolarization occurs within the cerebellar cortex [7]. The action of γ-aminobutyric acid (GABA) is another example. Several conclusions have been drawn in this report from experiments of topical application of GABA. However, a different interpretation of these findings has been recently advanced [8]. Moreover further possibilities of testing Purpura's hypothesis with GABA may be provided by the observation that strychnine "spikes" are absent not only in the cerebellum but also in the olfactory bulb [9].

French reviews the corticifugal connections of the reticular formation, a problem which has been studied with success by him and other investigators in Magoun's laboratory. EEG arousal can be obtained by stimulating those areas of the cerebral cortex, and those areas only, which project onto the reticular formation. Investigations on monkeys with implanted electrodes show that EEG activation parallels behavioural arousal. Low intensities of stimulation elicit behaviour suggesting alertness, while stronger stimuli evoke reaction patterns indicating fear.

The physiology of the descending reticular system is reviewed by Ward and by Eldred and Fujimori. Eldred and Fujimori are concerned with the reticular areas whose stimulation influences spindle activity. They state that stimulation of several regions of the reticular formation yields non-reciprocal, bilaterally symmetrical facilitation. Contrary to expectation, they report facilitation of muscle spindles following stimulation of Magoun's bulbo-inhibitory center.

Several studies are devoted to the relationships between the reticular formation and endocrine activity. Harris points out that the reticular formation may influence the hypophysis via (i) the rich fiber connections between the midbrain and the tuberal area of the hypothalamus, and (ii) a more circuitous route involving the archipallium. He reports on his important experiments dealing with the influence of the hypothalamus on pituitary thyrotropic secretion and on sexual behaviour. According to Sawyer progesterone markedly influences the reticular threshold for EEG and behavioural arousal of the castrated female rabbit. Hume is concerned exclusively with the hypothalamus and the localization of the zones controlling the secretion of corticotropin, thyrotropin and gonadotropin.

Neuropharmacology is represented by the contributions of K.F. and E.K. Killam, of Bradley and of Domino. The Killams show that, in sharp contrast with barbiturates, mephenesin blocks both recruiting and EEG arousal responses elicited by stimulating the thalamus, but not the EEG arousal produced by reticular stimulation. Tranquilizing agents like chlorpromazine and reserpine have no effect on reticular and thalamic arousal in the curarized cat, although in the spontaneously sleeping animal chlorpromazine markedly raises the thalamic thresholds both for EEG and, to a higher degree, for behavioural arousal. The reticular stimulation effects on EEG are, however, not influenced by the drug in the spontaneously sleeping cat, while those on behaviour are only slightly depressed.

The possibility of using drugs to dissociate EEG from behavioural arousal, or thalamic from reticular effects, is from the neurophysiologist's standpoint perhaps the most important contribution of neuropharmacology to this field of investigation; and much work has been carried out since Wikler's discovery of the striking dissociating effects of atropine. This

---

1 BREMER, F. *Arch. int. Physiol.*, **1925**, *25*: 131.
2 MORUZZI, G. *Arch. Fisiol.*, **1936**, *36*: 408, and **1941**, *41*: 183.
3 TERZUOLO, C. *Arch. int. Physiol.*, **1954**, *62*: 179.
4 See DOW, R. S. and MORUZZI, G. *Cerebellum: Physiology and Pathology*. Minneapolis, University of Minnesota Press, **1958**.
5 ROSSI, G. *Arch. Fisiol.*, **1912**, *10*: 384.
6 CANESTRARI, R., CREPAX, P. and MACHNE, X. *Arch. psicol. neurol. psich.*, **1955**, *16*: 19.
7 GRANIT, R. and PHILLIPS, C. G. *J. Physiol.*, **1956**, *133*: 520.
8 JASPER, H., GONZALES, S. and ELLIOTT, K. A. C. *Fed. Proc.*, **1958**, *17*: 79.
9 FRANKENHAEUSER, B. *J. Neurophysiol.*, **1951**, *14*: 73.

field has been thoroughly studied by Elkes and Bradley and the results of their work is reported. Bradley makes a distinction between the drugs (like physostigmine and atropine) whose effects on electrical activity do not correlate with behaviour and those (amphetamine and LSD 25) which exert a parallel effect. The effects of the first group of drugs are unchanged by brain stem transections, while the action of amphetamine is absent in the *cerveau isolé*, and that of LSD 25 is absent in the *encéphale isolé*.

Domino reports on an interesting pharmacological dissociation between the ascending and descending components of the reticular system. The EEG flattening elicited by reticular stimulation, in the chloralosed cat, is not depressed, but occasionally enhanced, by doses of a centrally acting muscle relaxant, zoxazolamine, which markedly reduces the effect on the patellar reflex. While reviewing the action of chlorpromazine on postural extensor tonus, he fails to quote an important paper, probably because it had been published shortly before the Symposium. Henatsch and Ingvar (1956) have shown that chlorpromazine abolishes γ but not α rigidity, an observation that may throw much light on the neural mechanism of this drug.

Three papers are devoted to the relations between the reticular formation and problems of experimental psychology. Lindsley's investigations on the perceptual process are of the greatest importance. By studying the responses evoked by photic stimuli, he first shows that visual cortex activity is the limiting factor in determining critical flicker frequency. Another time-limited phenomenon is the discrimination of two brief flashes of light from one. It may be studied electrophysiologically by measuring the minimum time interval between a pair of flashes which still evoke two distinct potentials in the visual cortex. Lindsley shows that following reticular stimulation the visual cortex of the cat is able for several seconds to resolve separate responses to two flashes, while only one potential is evoked in the absence of such stimulation. These results correlate very satisfactorily with the microelectrode studies of Jung, which were reported above. Other stimulating experiments are those performed in Lindsley's laboratory by Fuster, who found, in tachistoscopic experiments with the monkey, that a statistically significant increase of the percentage of correct responses and a decrease in the mean reaction time occurred during reticular stimulation. Investigations on man showed that the mean reaction time is increased when the subject has been alerted in advance to the presentation of the visual stimulus. This effect is particularly marked with a fore-warning of 300 to 1000 msec., i.e. when the visual stimulus is applied during the α blockade.

Morrell and Gastaut report on their EEG investigations of conditioned reflexes, and Gastaut develops his well-known hypothesis on the neural mechanisms of conditioning. The vastness of this theme makes it impossible to summarize their reports within the limit of space allotted to this review. However, several aspects of them are already known to readers of the Journal [1].

Space limitations also prevent a detailed analysis of those papers whose theme was not strictly related to that of the Symposium, although several observations reported therein deserve the greatest attention. Brazier was concerned with the neural responses evoked by light flashes, Li with the activity of the interneurons of the motor cortex, while Ingram dealt with the effects of hypothalamic lesions on learning. The last part of the book was devoted to the visceral brain or rhinencephalon. Papez presented an anatomical introduction, while Green, Adey and Mason elaborated on different aspects of the physiology of these structures. The same regions of the brain were studied by Olds, who described his fascinating experiments on self-stimulation in rats, a technique which was also utilized by Brady in the experiments on cats and monkeys which he reported in this Symposium. Finally Lilly described his investigations on the effects of electrical stimulation in the unanesthetized monkey. Some of the experiments reported by Adey, such as the effects of stimulation of the entorhinal area on the spike discharges of the midbrain tegmentum and on reticular conduction, appear to be closely connected to the main theme of the Symposium.

The final report of the Symposium was made by Jefferson, who dealt with the relevance of the reticular formation for clinical neurology. His observations on the "anterior critical point", which has a profound effect on consciousness when damaged or compressed, despite the fact that the main activating systems are intact, should provide a stimulus for experimental investigation. Gerard then summarized in his usual vivid way the general results of the Symposium.

The banquet speech by Penfield, with which the book ends, charmingly evokes in the mind of the reader the spirit of Hippocrates, and the dawn of medical inquiry (as well as of our civilization) in the Aegean Islands. Penfield notes, "the truth, Hippocrates wrote, is to be learned by observation of nature. Authority is to be found in the working of body systems and in their behaviour during health

---

1 GASTAUT *et al. EEG Clin. Neurophysiol.*, **1957**, *9*: 1.

and diseases — not in the hypotheses of the Philosophers.'' These thoughts still ring true and suggest a note of caution that is valid even to-day. We know, of course, that hypotheses are essential for the development of science, but we must always guard against our own tendency to regard them as established facts. This usually happens when a given view becomes deeply rooted in our minds, either because it has been accepted widely and silently for several years or because of the fact that it has proved its usefulness by promoting important investigations. A distinction between facts and hypotheses is obviously more difficult to make when scientific research is going on intensively in a given field of investigation. It is not surprising, therefore, that such a tendency is apparent when one reads the proceedings of the Detroit Symposium, and that occasionally it creeps even into the titles of the articles. Indeed, even some of our terminology in this field is actually the expression of hypotheses, so that an attempt to clarify our thoughts may perhaps not be out of place, although it may lead to repetitious statements.

Let us start with neuroanatomy and the somewhat loose way the adjective ''reticular'' is being used in the neurological literature. That the midline nuclei of the thalamus, and Dempsey and Morison's recruitment phenomenon, are under reticular control seems a well established fact, but to refer to the unspecific thalamic nuclei as the thalamic portion of the reticular system or the thalamic reticular system is an extrapolation that perhaps is not wholly justified by the available evidence. It may be actually misleading, since it is likely to give the impression that the reticular connections with the hippocampus or with the caudate nucleus are physiologically less important. All we can say, at the present, is that our knowledge on the latter group of interrelations is much less satisfactory than that on the thalamo-reticular relationships. This disproportion in the growth of our knowledge is, however, a contingent fact, one that may be easily explained historically, since the study of the sphere of influence of the reticular formation was bound to start with those thalamic structures whose function had been disclosed by the fine work of the Boston and Montreal Laboratories.

Similar considerations apply when we consider the functional significance of the ascending reticular system. There is a growing tendency to include more and more functions within its sphere of influence. For example there is little doubt that transmission in subcortical relays as well as the evoked potentials of the cortical sensory areas are affected by reticular stimulation, and it is an indisputable fact, and a fundamental observation, that these processes are strongly modified during habituation and attention. However, there is no crucial proof that the afferent block occurring during habituation is mediated by the reticular formation. Indeed some data against this interpretation have been noted above. Along the same line of thought, a distinction should be made, when dealing with Pavlovian physiology, between a phenomenon such as the EEG arousal occurring during the orienting reflex, whose relationship with the reticular formation is certain, from the hypotheses on the development and extinction of conditioned reflexes or on the sleep elicited by monotonous stimuli, which still await crucial proof.

Finally, the neuropharmacological evidence. The fact that a drug has an influence on EEG synchronization or that it affects sensory or reticular arousal does not imply, necessarily, a central action on the reticular formation. For some drugs this influence has been demonstrated in several ways, such as by studying their effect following brain stem transections at different levels or by recording their influence on the spontaneous spike discharge or evoked responses of the reticular formation. But even then it may occasionally be premature to attribute the effects of these drugs to a selective influence solely on the reticular formation.

Books of this kind should be evaluated in terms of the stimulus to research which the reader receives while perusing them. From this point of view this Symposium was undoubtedly a success and the organizers should be congratulated for the results of their endeavour. Since Symposia are going to become more and more important as a mean of interdisciplinary communication, future organizers should be warned against their inherent tendency to grow in size. One of the weak points of the Detroit Meeting is represented by the obvious disproportion between the time allotted to the reports and that left for the discussion, which was often neglected. This is perhaps the consequence of the large number of reports and of the multiplicity of themes.

From the point of view of the art of book making this is an esthetically attractive volume. Topographical errors or inconsistencies of nomenclature are always present in a collaborative work of this size. Several names are mispelled, apparently because they were handled phonetically so that ''Machne'' becomes ''McNey'', ''Lilly'' becomes ''Lillie'', etc., while the famous anatomist Elliot Smith becomes Smith and is quoted as Smith, G. E. (pp. 621, 622). This error and others, like ''mammary bodies'' instead of ''mammillary bodies'' (p. 62) or ''Areau rhythm'' instead of Gastaut's rolandic *rythme en arceau* (p. 589), might perhaps have been avoided.

Giuseppe MORUZZI

L'ELETTROENCEFALOGRAFIA CLINICA

(con particolare riferimento alle lesioni a focolaio)

CARLO PERRIS

Ed. ''Omnia Medica'', Pisa, Italy, 1957, 264 pp. Approx. $4.00

This is one of several monographs on clinical EEG which has appeared in the Italian literature in the last five years. Although all the authors have a relatively limited experience in the subject, this productivity may be optimistically viewed as a result of the enthusiasm with which young investigators enter the field of electroencephalography.

In Perris' monograph, as the subtitle indicates, the main emphasis is on ''focal lesions'', and in particular, on the EEG aspects of brain tumors. The book is divided into two parts consisting, respectively, of 12 and 6 chapters. The first two chapters deal very briefly and rather superficially with the physiological basis of EEG, with technical problems and with the general technique of recording used by the author. The subsequent chapters in part 1 consist of a fairly complete, though rather uncritical review of the literature on the following subjects: (*a*) normal rhythms (description and topographical distribution); (*b*) conditions known to influence the EEG (age, wakefulness and sleep, temperature, blood sugar, etc.); (*c*) activation procedures (subdivided into chemical and physical); (*d*) abnormal rhythms (morphology and criteria for their localization); (*e*) most common abnormalities seen in cases of brain tumors both in proximity to the lesion and at a distance from it; (*f*) possibility of EEG diagnosis of nature in cases of expanding lesion; (*g*) possibility of brain tumor localization with EEG, and (*h*) criteria for differential diagnosis and for prognosis.

In the second part (about 50 pages) the author presents his own material correlated by several useful summarizing tables.

The general presentation is rather uneven. For instance, the author goes into a long, detailed description of the various types of electrodes, including those very seldom used or only presenting some theoretical interest, yet he is rather vague as far as the electrode position in the scalp is concerned. In fact, electrode position and electrode run are terms used at times interchangeably (see i.e. fig. 22 showing ''electrode runs'' according to Jasper). Three schematic sketches are presented in chapter II, for illustrating the electrode runs. These include a ''standard'' (unipolar to ipsilateral ear) ''Walter'' (bipolar antero-posterior combined with transversal) and a ''circular'' run. Throughout the text, and in the illustrations, other runs are mentioned (''transversal'' and ''longitudinal''). Notwithstanding long discussions on the advantages to study phase reversal, and on the usefulness of recording simultaneously from pairs of electrodes perpendicularly oriented to each other, about half of the fifty samples of EEG tracings presented are with the ''unipolar'' technique. In 10 per cent, there is no indication on the run used, and in another 10 per cent the labels are hardly readable. In fact, the inadequacy of the legends in most of the samples and the impractical method of explaining the run used are one of the weak points of the book.

On the other hand, rather useful is a summarizing table of the percentages of localization in case of brain tumors obtained by the various authors between 1946 and 1953, which also includes the number of cases in each study, as well as the type of localization of the expanding process.

The original contribution in the monograph consists of the presentation and discussion of 80 cases, 67 having a definite, and 13 an approximate diagnosis of brain tumor and in which, from a clinical standpoint, 42 localizations and 17 lateralizations were possible in one group and 11 localizations in the other group.

From an X-ray standpoint, 17 showed general signs, 12 suggestive signs, and 17 specific signs of brain tumor; in 3 the signs were specific but pointing to the wrong side; the remaining 30 were normal. Electrographically, it was possible to make a diagnosis of brain tumor in 72 cases, while in the remaining 8 the EEG changes were ''aspecific''. Of the cases in which a diagnosis of brain tumor was possible, there were 11 lateralizations, 13 suggestions of localization and 45 good localizations (37 exact and 8 approximate). In 3 the EEG provided wrong localization.

Twenty one cases were tumors of the middle fossa, of the basal nuclei, of the pontocerebellar angle, of the 3rd ventricle or sellar region and of the cerebellum. For each of these, the author reports in detail the EEG findings with only a brief comment on the tendency of the parasellar tumors to show a predominance of bi-parietal alterations with shifting character. At the end the author describes six ''characteristic patterns'' which, in his opinion, should be specific for brain tumors. These are various types of more or less irregular delta and theta waves and of some sharp transients, either appearing in the ''pure'' form or intermixed, and for which the separation into six different patterns attempted by the author appears highly

artificial. He, himself, states that they may often coexist in the same tracing. In his experience epileptiform potentials were seen in 41 cases, always contralateral to the side of the tumor; these, in his opinion, are "more prevalent when using transversal runs than when using longitudinal runs".

The book contains, unfortunately, numerous errors, some obviously due to inadequate care in proofreading (i.e. on page 49, "14,000 c/sec. rhythm present in the cortex"; on page 221, "33 wrong localization in 72 cases of tumors"; on page 85, "*of* effect" instead of "on effect", etc.); others due to inaccurate or superficial survey of the literature or to lack of clear concepts.

Rather surprising is in fact to find electroencephalographers who still ignore the existence of Caton (page 11, "it is, however, right to remember that it was Prawdicz-Neminski who first demonstrated — 1913-1925 — the existence of spontaneous electrical activity in the cerebral cortex"). Elsewhere, the time constant is defined as the "time taken for a voltage passing through a resistence - capacity system to drop *of* 1/e (37%) of its initial value". In the description of the various patterns elicitable with intermittent photic stimulation, it is stated that one may observe "a response only at the end of the stimulation (comparable to the on effect of the peripheral nerve stimulation)". On the same subject, several findings are reported as pure result of intermittent photic stimulation without taking into account that they were, instead, obtained using Metrazol associated with it. In discussing the 3/sec. spike-and-wave complexes, the author states that they are "favored by hyperventilation and by the blocking reaction" (?).

Elsewhere the author quotes and accepts the statement of Strauss *et al.* that "a normal EEG during an epileptic seizure precludes the diagnosis of epilepsy", etc.

Notwithstanding the presence of these and other inaccuracies, it is obvious that the author has made a sincere effort to cover, as completely as possible, the field of EEG in brain tumors, and in fact, he has succeeded in completing a work which should prove of some usefulness to neurologists and electroencephalographers. An extensive bibliography (including a number of Italian authors with whom the American reader may be unfamiliar) at the end of the book is arranged under the heading of each chapter to which it refers. By this method repetitions are unavoidable but its use is more convenient and practical.

C. AJMONE-MARSAN

THE BRAIN AND HUMAN BEHAVIOR

(Proceedings of the Association for Research in Nervous and Mental Disease, Volume XXXVI)
The Williams & Wilkins Company, Baltimore, 1958, 564 pp., $15.00

The work under review, the Ciba symposium (1958), the symposium of the New York Academy of Sciences (66: 417, 1957) and the Wisconsin symposium (1958) reflect the intensity of the work concerned with the neurophysiological and biochemical foundations of behavior. It seems to the reviewer that the Ciba symposium attacks these problems on a broader basis, and that the selection of topics from an anatomical viewpoint for the symposium of the Association for Research in Nervous and Mental Disease was rather unfortunate. Nevertheless, the 21 contributions present a rich fare.

The function of the temporal lobe is subjected to a detailed analysis. Penfield gives a fascinating review of his studies on memory and the production of illusions and hallucinations. This is an outstanding contribution regardless of whether one takes seriously the author's attempt to relate these complex functions to the centrencephalic system. Bickford *et al.* supplement this work by showing that stimulation through depth electrodes may produce temporary amnesia when the tip of the electrode is in the vicinity of the hippocampus. Chapman and also Jasper and Rasmussen stimulate the amygdala and hippocampus in patients with assaultive behavior and epilepsy, respectively. Gibbs reports his wellknown work on the EEG changes in epilepsy of the temporal lobe and stresses the significance of the sleep record for diagnosis and the relation between age and the locus of abnormality in the temporal lobe. Green *et al.* find that anterior temporal lobectomy in patients with focal epilepsy causes, in the successful cases, a marked improvement in affective responses, while Milner, on the basis of more extensive unilateral ablations of the temporal lobe, comes to the important conclusion that defects in the dominant left lobe lead to difficulties in understanding and retention of ''verbally expressed ideas'', whereas similar lesions in the non-dominant side are accompanied by disturbances in the perception of ''pictorially expressed ideas''. The interesting work of Bremer on the transmission of sensory impulses via the corpus callosum is not unrelated to this group of papers since it deals with the neurophysiological basis of the fundamental studies of Myers and Sperry on ''contralateral mnemonic effects with ipsilateral sensory inflow''.

The neuropharmacological investigations presented by Hoch from the clinical and by Evarts from the experimental point of view show how far we are removed from an understanding of the action of drugs such as ISD. Evarts' statements that such studies ranged from psychoanalysis to work on the clam suggest that more than broadness of approach is needed for the solution of these problems.

Of the remaining group of papers dealing with quite diversified aspects of the problem of behavior, I mention Woolley's challenging studies on serotonin; Feldberg's work on the intraventicular action of drugs such as adrenaline and DFP; Roberts' observations on recovery of speech after cortical lesions, and the interesting studies of Wolff *et al.* showing, on the basis of extensive psychological testing of cases with cerebral defects, the importance of the mass effect rather than that of the side or site of the lesion; Lacey's successful attempt to relate the frequency of autonomic discharges to impulsivity and to neurophysiological theory; Bruner's suggestions, based on spychological data, concerning the physiological mechanisms underlying complex perceptual processes; Nielsen's emphasis on the relation between the central autonomic system and the psychoses.

Attention is called to Denny-Brown's painstaking analysis of grasping, placing and avoidance reactions in monkeys with a variety of parietal lesions. A major factor in normal behavior seems to be the balance between the ''positive exploratory mechanism'' of the parietal lobes involving tactile and visual perceptions and the avoidance reactions greatly exaggerated in the frontal-insular animal (parietal, occipital and temporal lobes removed).

These and other investigations show that progress is made in this complex area without consideration of the time honored mind-body problem, but Lashley's discussion of this question presented in the first article (''Cerebral Organization and Behavior'') with insight and vigor, makes this book memorable.

This and other symposia on closely related topics offer an opportunity to compare the effectiveness of various methodological approaches and to appreciate the difficulties in evaluating experimental data obtained from patients with different kinds of brain pathology and/or different premorbid personalities to mention only two factors. Like other books written by numerous contributors it suffers from the lack of a leading idea (''If a book is to have value except as a work of reference it must be the work of one mind'' B. Russell), but the data are being accumulated and wait for the fertile mind.

E. GELLHORN

INDEX TO CURRENT LITERATURE

Edited by CHARLES E. HENRY
Institute of Living, Hartford, Conn., U.S.A.

AHRENS, R. und RADKE, H. Der Einfluss von Reserpin und Megaphen auf den gaövanischen Hautreflex und das EEG. *Acta neurovegetativa,* **1958**, *14*: 53-67.

ALAJOUANINE, TH., THUREL, R., HOUDART, R. et NEHLIL, J. La lobectomie temporale dans le traitement de l'épilepsie psychomotrice: Indications électro-cliniques; corticographie; résultats. *Encéphale,* **1958**, *47*: 265-308.

ALCARAZ, M. y GUZMÁN, C. Interacción de los potenciales evocados en las áreas específicas visual y auditiva. *Bol. Inst. Estud. méd. biol. Méx.,* **1958**, *16*: 21-27.

ANASTASOPOULOS, G., DIACOYANNIS, A. et ROUTSONIS, K. Bégaiement et épilepsie temporale. *Rev. Neurol.,* Paris, **1958**, *99*: 472-479.

ARMINGTON, J. C., BIERSDORF, W. R. and MAILLOUX, L. D. An apparatus for scoring electroencephalograms. *Amer. J. Psychol.,* **1958**, *71*: 594-599.

ASCIONE, A., COLTORTI, M., SERRA, C. e LAMBIASE, M. Aspetti elettromiografici ed elettroencefalografici delle malattie del collageno. *Gior. clin. Med.,* **1958**, *39*: 1819-1847.

BALLABRIGA, A., SAMSO, J.-M. et VILA-BADO, A. Etude expérimentale de l'anoxie fœtale et du nouveau-né. *Et. Néo-Nat.,* Paris, **1957**, *6*: 116-133.

BANCAUD, J. L'utilisation de l'examen psycho-pathologique dans l'interprétation du tracé EEG des tumeurs intracraniennes. (Thèse, Paris), **1958**, 130 pp.

BEHRMAN, S. and WYKE, B. D. Vestibulogenic seizures. A consideration of vertiginous seizures, with particular reference to convulsions produced by stimulation of labyrinthine receptors. *Brain,* **1958**, *81*: 529-541.

BISHOP, G. H. The relation between nerve fiber size and sensory modality: Phylogenetic implications of the afferent innervation of cortex. *J. nerv. ment. Dis.,* **1959**, *128*: 89-114.

BOBKOVA, V. V. [Electrophysiologic study of motility disturbances in hysteria.] *Nevropat. Psikhiat.,* Moskva, **1958**, *58*: 1285-1292.

BORGNA, E. e MARINATO, G. Osservazioni psicopatologiche, neurologiche ed elettroencefalografiche in malattie flogosiche del sistema nervoso centrale trattate con ormone adrenocorticotropo e cortisonici. *Med. Psicosomat.,* Roma, **1958**, *3*: 219-243.

BÖSZÖRMÉNYI, Z., DÉR, P. and NAGY, T. Observations on the psychotogenic effect of N-N diethyltryptamine, a new tryptamine derivative. *J. ment. Sci.,* **1959**, *105*: 171-181.

BOUDIN, G., BARBIZET, J. et MASSON, S. Etude de la dissolution de la conscience dans 3 cas de petit mal avec crises prolongées. *Rev. Neurol.,* Paris, **1958**, *99*: 483-487.

BOWER, B. D. and JEAVONS, P. M. Infantile spasms and hypsarrhythmia. *Lancet,* **1959**, *1*: 605-609.

BROOKHART, J. M., ARDUINI, A., MANCIA, M. and MORUZZI, G. Thalamocortical relations as revealed by induced slow potential changes. *J. Neurophysiol.,* **1958**, *21*: 499-525.

COHN, R. and ULSHAFER, T. R. Electroencephalograph correlates of ammonium carbonate intoxication in the rat. *Nature,* **1958**, *182*: 1735-1736.

COLLOMB, J., BERT, J., PLAS, R. et LAURENT, J. L'électroencéphalographie des états délirants et hallucinatoires aiguë chez le jeune adulte. *Ann. méd. psychol.,* **1959**, *117*: 461-470.

DE GERSCHENFELD, D. J. y MULLER, A. O. Lipoma del cuerpo calloso. Estudio radiológico y electroencefalográfico. *Acta Neuropsiq.,* Argentina, **1958**, *4*: 285-289.

DESMEDT, J. E. and MECHELSE, K. Suppression of acoustic input by thalamic stimulation. *Proc. Soc. Exp. Biol.,* N.Y., **1958**, *99*: 772-775.

DE VALOIS, R. L., SMITH, C. J., KAROLY, A. J. and KITAI, S. T. Electrical responses of primate visual system: I. Different layers of macaque lateral geniculate nucleus. *J. comp. Physiol. Psychol.,* **1958**, *51*: 662-668.

DOLMIERSKI, R. i KLOSSOWNA, M. [On the disease of Gilles de la Tourett.] *Neurol. Neurochir. Psychiat. Polska,* **1958**, *8*: 639-646.

DOMŻAL, T. [Electroencephalographic examination of the pathogenetic specificity of migraine head pain.] *Neurol. Neurochir. Psychiat. Polska,* **1958**, *8*: 745-752.

DOTY, R. W. Potentials evoked in cat cerebral cortex by diffuse and by punctiform photic stimuli. *J. Neurophysiol.,* **1958**, *21*: 437-464.

EIDELBERG, E., FELDMAN, S. and MAGOUN, H. W. Role of gamma-aminobutyric acid in electrocortical arousal. *Neurol.*, **1959**, *9*: 15-17.

FALK, B., KIRSTEIN, L., LÖFSTEDT, L. and SILFVERSKIÖLD, B. P. Pneumoencephalographic investigations in epilepsy. *Acta psychiat.*, Kbh., **1958**, *33*: 440-451.

FERNÁNDEZ, A. y ROLDÁN, E. Efecto de la estimulación eléctrica de la corteza cerebral sobre unidades aisladas de la formación reticular mesencefálica. *Bol. Inst. Estud. méd. biol. Méx.*, **1958**, *16*: 59-73.

FERREIRA, M. R. Técnica original para implantação de eletródios corticais no cão. *J. Brasil. Psiquiat.*, **1958**, *7*: 117-134.

FOSTER, A. L. The relationship between EEG abnormality, some psychological factors and delinquent behavior. *J. Proj. Tech.*, **1958**, *22*: 276-280.

FOURMENT, A., LELORD, G., CALVET, J. et SCHERRER, J. Réponse électrocorticale visuelle et ses modifications par stimulations concomitante chez le lapin. *C. R. Soc. Biol.*, Paris, **1958**, *152*: 1680-1683.

FRANTZEN, E., HARVALD, B. and HAUGSTED, H. Fresh head injuries. Clinical and electroencephalographic studies on 399 patients. *Acta psychiat.*, Kbh., **1958**, *33*: 417-428.

FUNKHOUSER, J. B. and NAGLER, B. The electroencephalogram of multiple sclerosis. (A preliminary report). *Dis. nerv. Syst.*, **1959**, *20*: 41-44.

GARDE, A., DEVIC, M. et MULLER, J.-M. Les encéphalites subaiguës primitives de l'enfant. *Lyon méd.*, **1958**, *199*: 197-228.

GASTAUT, H., NAQUET, R., REGIS, H. et SALAMON, G. Sur les effets électrographiques d'une anoxie cérébrale de longue durée. *C. R. Soc. Biol.*, Paris, **1958**, *152*: 1251-1253.

GEISLER, E. und STADLER, H. Klinische Beobachtung und EEG-Veränderungen bei Megalencephalie. *Helv. Pædiat. Acta*, Basel, **1957**, *12*: 541-547.

GELLHORN, E. Hypothalamisch-corticale Beziehungen und ihre Bedeutung für die höheren Funktionen des Gehirns. *Nervenarzt*, **1958**, *29*: 385-392.

GIBBENS, T. C. N., POND, D. A. and STAFFORD-CLARK, D. A follow-up study of criminal psychopaths. *J. ment. Sci.*, **1959**, *105*: 108-115.

GOKHBLIT, I. I. Characteristics of sleep and waking electroencephalograms in dogs of different ages. *Bull. Exper. Bio. Med. USSR. Eng. Trans.*, **1958**, *46*: 790-794.

GOLDRING, S., METCALF, J. S., HUANG, S. H., SHIELDS, J. and O'LEARY, J. L. Pharmacological selectivity manifested by agents acting upon the cortical dendritic spike and its slow after-effects. *J. nerv. ment. Dis.*, **1959**, *128*: 1-11.

GREEN, J. D. A simple microelectrode for recording from the central nervous system. *Nature*, **1958**, *182*: 962.

GRÜSSER, O.-J. und GRÜTZNER, A. Neurophysiologische Grundlagen der periodischen Nachbildphasen nach kurzen Lichtblitzen. *Graefes Arch. f. Ophthal.*, **1958**, *160*: 65-93.

GRÜSSER, O.-J. und GRÜTZNER, A. Reaktionen einzelner Neurone des optischen Cortex der Katze nach elektrischen Reizserien des Nervus opticus. *Arch. f. Psychiat. Z. Neurol.*, **1958**, *197*: 405-432.

GRÜTZNER, A., GRÜSSER, O.-J. und BAUMGARTNER, G. Reaktionen einzelner Neurone im optischen Cortex der Katze nach elektrischer Reizung des Nervus opticus. *Arch. f. Psychiat. Z. Neurol.*, **1958**, *197*: 377-404.

HAJNSEK, F. [Psychomotor epilepsy.] *Neuropsihijat.* Zagreb, **1958**, *6*: 22-36.

HATORI, S. Activating effect of photo-metrazol on the EEG of various psychoses and neuroses cases. *Folia Psychiat. Neurol. Jap.*, **1958**, *12*: 122-141.

HEATH, G. Correlation of electrical recording from cortical and subcortical regions of the brain with abnormal behavior in human subjects. *Confinia Neurol.*, **1958**, *18*: 305-315.

HIRSCH, J.-F. Réponses électriques corticales des animaux et de l'homme à une stimulation somesthésique. (Etude physiologique comparée des aires somesthésiques chez les mammifères.) (Thèse, Paris), **1958**, 188 pp.

JAYLE, G. E., BOYER, R. et CAMO, R. Adaptation rétinienne à l'obscurité et riposte électrique corticale. *C. R. Soc. Biol.*, Paris, **1958**, *152*: 1725-1729.

JOHN, E. R. and KILLAM, K. F. Electrophysiological correlates of avoidance conditioning in the cat. *J. Pharm. exp. Ther.*, **1959**, *125*: 252-274.

JOYNT, R. J. Micro-electrode studies of cerebellar electrical activity in the frog. *J. Physiol.*, **1958**, *144*: 23-37.

JUNG, R. Excitation, inhibition and coordination of cortical neurones. *Exper. Cell Res.*, **1958**, *Suppl. 5*: 262-271.

JUNG, R. Neuropharmakologie: Zentrale Wirkungsmechanismen chemischer Substanzen und ihre Neurophysiologischen Grundlagen. *Klin. Wschr.*, **1958**, *24*: 1153-1167.

KAJTOR, F. and SZÁRA, S. Electroencephalographic changes induced by dimethyl-tryptamine in normal adults. *Confinia Neurol.*, **1959**, *19*: 52-61.

KANN, J. Central nervous system disturbance and the behavior problem child. A therapeutic test of the findings. *Rev. Psychiat. Inf.*, Basel, **1957**, *24*: 161-176.

KENNARD, M. A. The characteristics of thought disturbances as related to electroencephalographic findings in children and adolescents. *Amer. J. Psychiat.*, **1959**, *115*: 911-921.

KIRSTEIN, L. and SILFVERSKIÖLD, B. P. A family with emotionally precipitated "drop seizures". *Acta psychiat.*, Kbh., **1958**, *33*: 471-476.

KLETZKIN, M. and SWAN, K. The effects of meprobamate and pentobarbital upon cortical and subcortical responses to auditory stimulation. *J. Pharm. exp. Ther.*, **1959**, *125*: 35-39.

KNOTT, J. R., CORRELL, R. E. and SHEPHERD, J. N. Frequency analysis of electroencephalograms of stutterers and nonstutterers. *J. Speech Hearing Res.*, **1959**, *2*: 74-80.

KORNMÜLLER, A. E. Zum Wesen der Epilepsie aus Grund einer Analyse des EEG. *Fortsch. Neurol. Psychiat.*, **1958**, *26*: 470-482.

KREINDLER, A., ZUCKERMANN, E., STERIADE, M. and CHIMION, D. Electroclinical features of convulsions induced by stimulation of brain stem. *J. Neurophysiol.*, **1958**, *21*: 430-436.

KRUMP, J. E. Die Lebenswandlung des Elektroenzephalogramms bei Herz- und Kreislaufkranken. *Verh. dtsch. Ges. KreislForsch.*, **1958**, *24*: 258-265.

LAIDLAW, J. The application in general medical conditions of a visual method of assessing and representing generalized electroencephalographic abnormalities. *J. Neurol. Neurosurg., Psychiat.*, **1959**, *22*: 69-76.

LELORD, G., FOURMENT, A., CALVET, J. et SCHERRER, J. Le conditionnement de la réponse évoquée électrocorticale chez l'homme. *C. R. Soc. Biol.*, Paris, **1958**, *152*: 1097-1100.

LUTTRELL, C. N., BANG, F. B. and LUXENBERG, K. Newcastle disease encephalomyelitis in cats. II. Physiological studies on rhythmic myoclonus. *Arch. Neurol. Psychiat.*, Chicago, **1959**, *81*: 285-291.

MACLEAN, P. D. Contrasting functions of limbic and neocortical systems of the brain and their relevance to psychophysiological aspects of medicine. *Amer. J. Med.*, **1958**, *25*: 611-626.

MAGRI, R. e GIANNELLI, A. Sintomatologia neuro-psichica ed alterazioni elettroencefalografiche da iperinsulinismo spontaneo. *Riv. Patol. nerv. ment.*, **1958**, *79*: 827-850.

MARTIN, F. et de SEPIBUS, C. Traitement d'urgence des accidents toxico-allergiques en cours de traitement antiépileptique. *Rev. med. Suisse rom.*, **1958**, *78*: 639-659.

MARTINI, F., ANGELERI, F. e BIAGIOTTI, F. Ricerche cliniche, elettroencefalografiche e psicometriche sull'effetto dell' iproniazide (Marsilid) nei malati depressi. *Riv. Neurobiol.*, Perouse, **1958**, *4*: 283-314.

MELNITCHIOUK, P. V. [The application of rhythmic light stimulation to the acute period of the closed head wound for the study of cerebral activity in children.] *Nevropat. Psikhiat.*, Moskva, **1958**, *58*: 823-829.

MOTOKAWA, K., OIKAWA, T. and OGAWA, T. Midbrain response to electrical stimulation of the optic nerve. *Toboku J. exp. Med.*, **1958**, *69*: 79-88.

MULLAN, S. and PENFIELD, W. Illusions of comparative interpretation and emotion. Production by epileptic discharge and by electrical stimulation in the temporal cortex. *Arch. Neurol. Psychiat.*, Chicago, **1959**, *81*: 269-284.

MURAMATSU, T., ANDO, M., NAGATSU, T. and YAGI, K. Effects of flavin monosulphate and flavin adenine dinucleotide on the electroencephalogram. *Nature*, **1958**, *182*: 457-458.

NAQUET, R. et HARTUNG, L. Etude électroencéphalographique chez l'Homme de l'anesthésie provoquée par injection intraveineuse de méthitural (thiogénal). *C. R. Soc. Biol.*, Paris, **1958**, *152*: 1257-1260.

NARBOUTON, R. Contribution à l'étude des troubles du comportement chez l'enfant. (Recherches de corrélations électroencéphalographiques.) (Thèse, Paris), **1958**, 94 pp.

PAMPIGLIONE, F. and POST, F. The value of electroencephalographic examinations in psychiatric disorders of old age. *Geriatrics*, **1958**, *13*: 725-732.

PHILLIPS, P. B. and ZARIELLO, J. J. Epileptiform seizure and low G tolerance. A case report. *J. Aviat. Med.*, **1959**, *30*: 35-37.

RAMON-GUERRA, A. U. y GARCIA AUSTT, E. El electroencefalograma en las toxicosis del lactante. *Arch. Pediat.*, Uruguay, **1958**, *29*: 5-19.

REINERT, R. E. EEG changes with promazine. *Amer. J. Psychiat.*, **1959**, *115*: 742-743.

REVITCH, E. Psychomotor paroxysms of non-epileptic origin. *Dis. nerv. Syst.*, **1958**, *19*: 562-566.

ROBERTS, A. C. Symbolic language discrimination in psychomotor epilepsy. *Dis. nerv. Syst.*, **1958**, *19*: 469-475.

ROSS, G. S. and MORRELL, F. Electroencephalographic activation with combined sodium amytal and Metrazol. *Neurol.*, **1959**, *9*: 126-132.

SELLEY, I. Acute psychosis after head injury in children. *Acta psychiat.*, Kbh., **1958**, *33*: 208-218.

SILVERMAN, D., GROFF, R. A. and SAGEN, W. Clinical and electrographic studies in spontaneous intracerebral hematoma. *Neurol.*, **1959**, *9*: 75-81.

SMITH, C. M. and SCHNEIDER, R. A. Narcolepsy and hypoglycemia. *J. ment. Sci.*, **1959**, *105*: 163-170.

SNYDER, C. H. Epileptic equivalents in children. *Pediatrics*, **1958**, *21*: 308-318.

STEVENSON, G. C., COLLINS, W. F., RANDT, C. T. and SAURWEIN, T. D. Effects of induced hypothermia on subcortical evoked potentials in the cat. *Amer. J. Physiol.*, **1958**, *194*: 423-426.

STORM VAN LEEUWEN, W., STERK, E. and ZIERFUSS, E. Therapeutic effect of amphetamines in high doses in epileptic patients. Description of some cases. *Folia Psychiat. Neerl.*, **1958**, *61*: 649-651.

STOUPEL, N. Etude de l'interaction dans l'écorce d'influx thalamocorticaux spécifiques et non spécifiques. *Acta neurol. psychiat. Belg.*, **1958**, *58*: 759-771.

STREIFLER, M., FREUNDLICH, E. and BELLER, A. J. Electroencephalography in subdural hematoma and effusion in infants. *J. Dis. Children*, **1958**, *95*: 25-29.

STROBOS, R. R. J., ALEXANDER, E. and MASLAND, R. L. Brain tumor presenting as convulsive disorder. *Dis. nerv. Syst.*, **1958**, *19*: 518-522.

SUAREZ, M., TEIJEIRA, J. y SIERRA, G. Correlaciones clínico-bioelétricas de la acción de la vitamina B en las encefalopatías connatales. *Rev. Esp. Pediat.*, **1958**, *14*: 57-62.

TAKAHASHI, H., NAGASHIMA, A. and KOSHINO, C. Effect of γ-amino-butyryl-choline upon the electrical activity of the cerebral cortex. *Nature*, **1958**, *182*: 1443-1444.

TANGHERONI, W. e PARDELLI, L. L'EEG nell' età neonatale. I. Indagini sui prematuri e sugli immaturi. *Lattante*, Parma, **1958**, *29*: 7-18.

THIEBAUT, F., ROHMER, F., WACKENHEIM, A. et KURTZ, D. Les données EEG dans les hyperthyroïdies secondaires. *Pr. méd.*, **1958**, *66*: 1323-1326.

THIEFFRY, S. et AICARDI, J. Les spasmes en flexion du nourrisson. 36 observations. Etude clinique. *Sem. hôp.*, Paris, **1958**, *34*: 1167-1178.

TORRES, F., FRANK, G. S., COHEN, M. M., LILLEHEI, C. W. and KASPAR, N. Neurologic and electroencephalographic studies in open heart surgery. *Neurol.*, **1959**, *9*: 174-183.

TURNER, W. J. and MERLIS, S Effect of some indolealkylamines on man. *Arch. Neurol. Psychiat.*, Chicago, **1959**, *81*: 121-129.

TUVO, F. Tracciato EEG "senza onde" in grave encefalopatia infantile. *Riv. Patol. nerv. ment.*, **1958**, *79*: 955-960.

UKOLOVA, M. A. and BORDIUSHKOV, I. N. Implantation of electrodes in the brain of white rats in experiments of long duration. *Bull. Exper. Bio. Med. USSR. Eng. Trans.*, **1958**, *46*: 1023-1025.

VAN BUREN, J. M. Some autonomic concomitants of ictal automatis. A study of temporal lobe attacks. *Brain*, **1958**, *81*: 505-528.

VILLAVICENCIO, C. y CHIOFALO, N. El electroencefalograma en las hemorragias cerebrales. *Neurocirugía*, Chile, **1958**, *16*: 15-17.

VILLAVICENCIO, C., CHIOFALO, N. y GOMEZ, J. C. El electroencefalograma en las afecciones vasculares del encéfalo. *Neurocirugía*, Chile, **1958**, *16*: 9-13.

VITALE, A. La reazione di risveglio nell'EEG umano patologica. *Arch. psicol. neurol. psichiat.*, **1958**, *19*: 243-264.

VOGEL, F. *Über die Erblichkeit des Normalen Elektroenzephalogramms.* Vergleichende Untersuchungen an Ein- und Zweieigen Zwillingen. Stuttgart: Georg Thieme, Verlag, **1958**, 92 pp.

VON MURALT, A. *Neue Ergebnisse der Nervenphysiologie.* Berlin: Springer, Verlag, **1958**, 256 pp.

WENDER, M. i ZNAMIEROWSKA, M. [The problem of clinical and anatomo-pathologic diagnosis of sub-acute sclerotic leukoencephalitis.] *Neurol. Neurochir. Psychiat. Polska*, **1958**, *8*: 423-434.

WHITE, R. P. and DAIGNEAULT, E. A. The antagonism of atropine to the EEG effects of adrenergic drugs. *J. Pharm. exp. Ther.*, **1959**, *125*: 339-346.

YUYAMA, T., YAMAMOTO, C. and IWAMA, K. Effects of repeated reinforcements upon electrical activities of the human brain in conditioned reflexes. *Folia Psychiat. Neurol. Jap.*, **1958**, *12*: 24-33.

ZANCHETTI, A. and BROOKHART, J. M. Cortico-spinal responsiveness during EEG arousal in the cat. *Amer. J. Physiol.*, **1958**, *195*: 262-266.

ELECTROENCEPHALOGRAPHY
AND
CLINICAL NEUROPHYSIOLOGY

AN INTERNATIONAL JOURNAL

Published by

THE INTERNATIONAL FEDERATION OF SOCIETIES
FOR ELECTROENCEPHALOGRAPHY AND CLINICAL
NEUROPHYSIOLOGY, Inc.

PARIS, 1949

Chief Editorial Office, 3801 UNIVERSITY ST. MONTREAL, CANADA

JOURNAL SUPPLEMENTS

No. 1. *Bibliography of Electroencephalography, 1875-1948,*
by MARY A. B. BRAZIER, Montreal, 1950. 178 pages, price $3.25.

No. 2. *Second International Congress Symposia,*
edited by H. FISCHGOLD, Paris, 1949. 137 pages (out of print).

No. 3. *Third International Congress — Communications,*
edited by R. SCHWAB, J. MERLIS, E. WALKER and C. HENRY, Cambridge, 1953.
94 pages, price $2.00.

No. 4. *Third International Congress — Symposia,*
edited by E. WALKER, J. MERLIS and C. HENRY, Cambridge, 1953.
260 pages, price $5.00.

No. 5. *Encéphalites et Encéphalopathies,*
by J. RADERMECKER, Masson & Cie, Paris, 1956. 243 pages, price $8.00.

No. 6. *Conditionnement et Réactivité en Electroencéphalographie* (Colloque de Marseille, 1955),
edited by H. FISCHGOLD and H. GASTAUT, Masson & Cie, Paris, 1957.
475 pages, price $15.00.

No. 7. *The Fourth International Congress of Electroencephalography and Clinical Neurophysiology with the First International Congress of Neurological Sciences, including the eighth Meeting of the International League against Epilepsy,*
Symposia and Proceedings, July 1957. 750 pages, price $15.00.

No. 8. *Electroencephalographic Researches in the Laboratories and Clinics of the Soviet Union,*
by V. S. RUSINOV and M. Y. RABINOVICH.
36 pages with 236 references, price $2.00.

No. 9. *The Sixth Annual Meeting of the Japanese EEG Society,*
Symposia and Proceedings, July 1957. Edited by TAKSHI MINOSHIMA.
141 pages, illustrated, price $2.00.

No. 10. *A Symposium on Dendrites*
Under the auspices of the American EEG Society,
ARTHUR WARD, J. Z. YOUNG, GEORGE BISHOP, HARRY GRUNDFEST.
Discussion by H. JASPER, M. and A. SCHEIBEL and others,
76 pages with 30 illustrations, price $2.00.

No. 11. *Obnubilations, Comas et Stupeurs*
Etudes Electroencéphalographiques par H. FISCHGOLD et P. MATHIS.
126 pages, 54 figures, price $8.00.

No. 12. *The Seventh Annual Meeting of the Japanese EEG Society*
and
The Eleventh Annual Meeting of the Japanese EMG Society
Symposium and Proceedings, July 1958. Edited by KENTARO SHIMIZU.
155 pages, illustrated, price $2.00.

No. 13. *The Moscow Colloquium on Electroencephalography of Higher Nervous Activity. October 1958*
Complete with illustrations and discussion.
Edited by G. D. SMIRNOV and H. H. JASPER. In press.

No. 14. *The Barbiturate Withdrawal Syndrome,*
A clinical and electroencephalography study by M. HERTEL WULFF, 1959.
173 pages with references and index, price $4.00.

Place your orders now with THE EEG JOURNAL
3801 University Street, Montreal 2, Canada